OriginalArticle

# Recent Trends In Nanoliposphere

**Abhiram Rout[1], Manmayee Mohapatra[2*],Ladi Alik Kumar[3], Sanjeeb Kumar Patro[4]**

[2*]Asst Professor, Gayatri Institute of Science and Technology, Gunupur, Odisha, India, Email Id-Manmayeemohapatra70@Gmail.Com, Contact No-8984369288
[3]Centurion University Of Technology And Management, Rayagada, Odisha, India
[1]Krishna Institute, Golbagh, Bijnor, UP, India
[4]College Of Pharmaceutical Sciences, Mohuda, Berhampur, Odisha, India

***Corresponding Author: -** Mrs. Manmayee Mohapatra

*Asst Professor, Gayatri Institute Of Science And Technology, Gunupur, Email Id-manmayeemohapatra70@Gmail.Com, Contact No-8984369288
**DOI:**10.47750/pnr.2022.13.S08.473

## Abstract

Background: Nanotechnology has generated a great deal of excitement worldwide and is being cited as the main technology ·of the 21st century. With the development of nanotechnology, the nanoliposphere has been increasingly viewed as a potential drug carrier for improving gastrointestinal absorption and oral bioavailability of some lipophilic drugs, offering multiple benefits in treating chronic human diseases by site-specific, and target-oriented delivery of specific medicines. Drug carrier systems are developed with the aim of varying the distribution of an active substance within the body and thus increasing the pharmacological efficacy and reducing its toxicity.

Methods: The recent advancement of Nanotechnology offers limited toxicity and can deliver drugs with low half-life or low therapeutic index for providing sustained or controlled drug delivery action.

Results: The usefulness of nanotechnology for multi-functionality of drug molecules, nanoliposphere play a promising role for attaining improved oral bioavailability of drugs for minimizing the adverse effects.

Conclusion: In this context, the present review article provides details on the preparation, future development, current status, Risk, and application of nanoliposphere-based drug delivery systems for oral bioavailability of drugs. Besides, the article aims to provide readers with an expert on current developments in nanoliposphere-based nanomedicines along with prospects with them in modern drug therapy.

**Keywords**: Drug targeting**,** Applications, innovation and processing, nanoliposphere, Drug delivery.

## INTRODUCTION

Nanoliposphere represent a new type of fat-based encapsulation system developed for parenteral and topical delivery of bioactive compounds and has been utilizing in the delivery of anti-inflammatory compounds, local anesthetics; antibiotics, anticancer agents, insect repellent, vaccines, proteins, and peptides. Composed of solid hydrophobic triglyceride particles and used as carrier materials for delivery of hydrophobic drugs loaded in it. ( 5 ) Various Processes such as solvent emulsification, evaporation, sonication, hot and cold homogenization, high-pressure homogenization, *etc*. have been reported in the literature for the development of Lipospheres. (6) Because the nanosize structure of the nanoliposphere also provides better permeability through a gastrointestinal barrier or stratum corneum for faster access to the desired target site.

### The benefits of the Nanoliposphere drug delivery system are;

- Improving drug stability
- Possibility for controlled drug release
- Controlled particle size
- High drug loading

### Advantages of Nanoliposphere drug delivery system

- High dispensability in aqueous medium
- Ease of preparation and scale up
- High entrapment of hydrophobic drugs
- Lipospheres exhibit enhanced physical stability due to avoidance of coalescence.
- Static interface facilitates surface modification of carrier particles after solidification of the lipid matrix.
- Low cost of ingredients.

### Disadvantages

- Physical instability in a liquid state
- Disruption in the stomach
- Difficulty in mass production and quality control
- Low drug loading capacity for protein.
- High pressure-induced drug degradation.
- Variable kinetics of distribution process

## APPLICATION OF NANOLIPOSPHERE(7)

### 1)Parenteral Route

• Nanoliposphere has been oppressed for the delivery of anesthetics like lidocaine bupivacaine, for the parenteral delivery of antibiotics like ofloxacin, norfloxacin, chloramphenicol palmitate, and oxytetracycline, and antifungal agents, such as nystatin and amphotericin B for the parenteral delivery of vaccines and adjuvant.

### 2)Transdermal route

• Properties like film forming ability, controlled release from solid lipid matrix ensuing in the extended-release of drug and retard systemic assimilation of drugs.

• Increasing the stability of drugs that are liable to extensive hepatic metabolism, makes them attractive candidates for topical delivery.

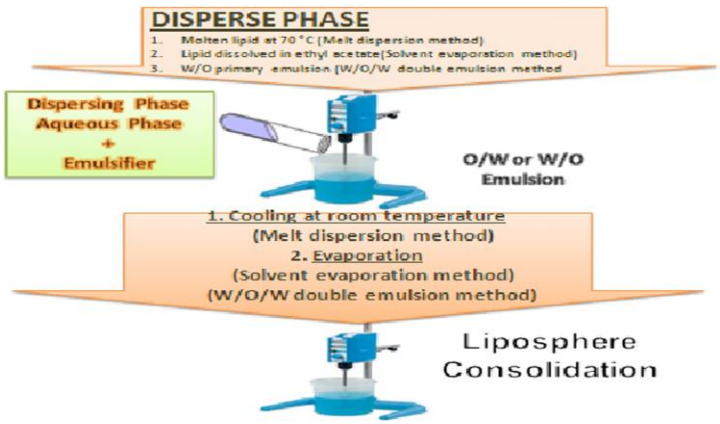
### 3)Oral delivery

• Numerous categories of drugs like antibiotics, anti-inflammatory compounds, anticancer agents, proteins, and peptides are being formulated as oral Nanoliposphere

## COMPOSITION AND CORE PRINCIPLES

Nanoliposphere is composed of a solid lipid core with a single layer of phospholipid containing drug enrich in it. Partition of the drug between lipids to form a uniform coat around the core is done by using a suitable emulsifier. The development of tensile strength of the external lipid coat is achieved by the addition of an aqueous plasticizer. For the perfection of hydrophilic drug entrapment w/o/w emulsion system was prepared and the drug release pattern of sodium cromoglycate was dependent on the type and nature of the selected stabilizer.( gelatin and poloxamer 407 ) used during formulation of them and show a sigmoidal pattern of drug release followed by consequent biphasic drug release behavior(11). The morphological personality of lipospheres can be subjective by the type and nature of the excipients, which will be liable to alter the shape, surface form, and other vital properties such as particle size, encapsulation efficiency, and drug loading. for example, Allopurinol is a highly lipophilic drug encapsulated in a lipid-based formulation containing beeswax, stearic acid, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol in combination with pluronic-68 as dispersant has shown smaller particle size remaining to the bees wax and stearyl alcohol content as a major contributing factor.(12) The use of phospholipids is one of the vital components of lipospheres which provide an external coat on them, thus mimicking the cellular structure. Examples of phospholipid (soya phosphatidylcholine and hydrogenated soya phosphatidylcholine) which are used as coating materials for extensive drug release applications. The reliability and physical stability of the lipospheres are dependent on the size of lipid particles and their surface charge on them. The effect of the nonionic surfactants shows significant influence in controlling the particle size, surface charge, and prolonged stability.(13) Thus, the study of the physical distribution of drugs in solid microparticles is also considered to be essential .

Cold and hot homogenization techniques are the two key processes that make use of regular live-out, which generate homogeneous matrix structure with active moiety present in the dispersed state as molecular forms or amorphous clusters. On the other hand, the drug-enriched shell type morphological structure shows the drug present inside the core, which provides a fall-apart release of the drug from the particle matrix. In the drug enriched core morphology, the drug is precipitated in the lipid shell and shows discharge by diffusion method.(14)




(**Fig. (1).** Techniques For Production Of Lipospheres By Melt Dispersion And Solvent Evaporation Techniques)

## Method for preparation of Lipospheres

### 1. Melt dispersion technique

- A combination containing all the phospholipids, cholesterol, etc, is arranged with and without a lipophilic model drug.
- The physical mixture is melted at 70°C and then emulsified into a hot external aqueous phase maintain at 60-70°C containing suitable surfactant.
- The emulsion is routinely stirred by using a mechanical stirrer equipped with swap impellers and maintained at 70°C, and a hot buffer solution is added at one time, along with the phospholipid powder.
- The hot mixture is homogenized for about 2 to 5 min, using a homogenizer or ultrasound probe, after which a uniform emulsion is obtained.
- The prepared emulsion is rapidly cooled to about 20°C by immersing the formulation into an ice bath and continuing the agitation to yield homogeneous dispersion of LS.
- The obtained LS is then washed with water and isolated by filtration through a paper filter.

### 2 . Solvent emulsification-diffusion technique

- The solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partly miscible with water and this method can be approved out either in the aqueous phase or in oil.
- firstly, both the solvent and water were commonly saturated to ensure the primary thermodynamic equilibrium of both liquids.
- while heating is required to solubilize the lipid, the saturation step was performed at that temperature.
- Then the lipid and drug were dissolved in a water-saturated solvent and this organic phase (internal phase) was emulsified with a solvent-saturated aqueous solution containing a stabilizer (dispersed phase) by using a mechanical stirrer.
- once the formation of o/w emulsion, water (dilution medium) in typical proportion range from 1:5 to 1:10, was added to the system to allow solvent diffusion into the continuous phase, thus forming an aggregation of the lipid in the nanoparticles (15).
- Here both the phase were preserved at the same elevated temperature and the diffusion step was performed either atroom temperature or at the temperature under which the lipid was dissolved.
- At some stage in the process, constant stirring was maintained.
- lastly the diffused solvent was eliminated by vacuum distillation or lyophilization.

### 3. Solvent evaporation technique

- This technique is a substitute for the melt dispersion technique and it is considered with the objective of possibly minimizing the exposure to high temperatures of thermo-labile compounds, such as proteins and nucleic acids.
- This technique is based on the evaporation of the organic solvent in which lipids are dissolved and allow the development of solid microparticles(15).
- In particular, the lipidic matrix is dissolved in an organic solvent such as ethyl acetate and maintained at the temperature of about 50-60°C and then emulsified with an external aqueous phase containing the surfactant agent.
- The resulting oil-in-water emulsion is stirred from 6 to 8 hr till the complete evaporation of the solvent.
- The LS is improved by filtration through a filter paper, dried and stored.

### 4. Rota evaporation method

- Here lipid solution with the drug is arranged in a round bottom flask containing 100 grams of glass beads (3mm in diameter) mixed carefully till a clear solution is obtained.
- Then, the solvent is evaporated by using a rotoevaporizer under reduced pressure at room temperature and a thin film is formed around the round bottom flask and the glass beads.
- Elevate the temperature up to 40°C until complete desertion of the organic solvent.
- Acknowledged amount of 0.9% saline is added to the vessel and the contents are mixed for 30min at room temperature then the temperature is lower to 10°C by insertion in an ice bath and mixing is continued for another 30min until lipospheres are produced(15).

### 5. Sonication method

- In this method, the drug is mixed with lipid in a scintillation vial which is already pre-coated with phospholipids.
- The vial is heated until the lipid melts, and then vortexes for 2min to make sure proper mixing of the ingredients.
- A 10 ml of hot buffer solution is added to the above mixture and sonicated for 10min with irregular cooling until it reaches room temperature (15).

### 6. Multiple microemulsion method

- This method in which a solution of the peptide is dispensed in stearic acid liquefy at 70ºC afterward, dispersion of this primary emulsion into an aqueous solution of egg lecithin, butyric acid, and taurodeoxycholate sodium salt at 70ºC.
- Rapid cooling of several emulsions formed solid Lipospheres with 90% entrapment of peptide.
- Constant release is reported by multiple emulsification techniques with the inclusion of lipophilic counter ion to form lipophilic salt of the peptide.

• Polymeric lipospheres have also been reported by double emulsification for encapsulation of antigen.

### 7 Ultrasonication or High-Speed Homogenization

• This technique is a dispersing technique, which was primarily used for the production of solid lipid micro or nanodispersion. Ultrasonication is based on the mechanism of cavitations.

· Steps-wise procedure is:

➢ The drug was added to earlier melted solid lipid then the heated aqueous phase (heated to the same temperature) was added to the melted lipid and emulsified by probe sonication or by using a high-speed stirrer or aqueous phase added to the lipid phase drop by drop followed by magnetic stirring.

➢ The obtain pre-emulsion was ultrasonicated using a probe Sonicated with a water bath (at 0ºC).

➢ Production temperature kept at least 5ºC above the lipid melting point to prevent recrystallization throughout the process. The obtained nanoemulsion (o/w) is then filtered through a 0.45μm membrane to remove impurities carried in during ultrasonication.

➢ The obtain SLN is stored at 4ºC. To increase the stability of the formulation it is necessary to lyophilize with the help of a lyophilizer to get the freeze-dried powder and for a time mannitol (5%) was added into SLNs as cryoprotection. (15)

### 8 Polymeric Liposphere

• Polymeric eco-friendly lipospheres can also be organized by solvent or melt processes.

• The variation between polymeric lipospheres and the standard liposphere formulations is the composition of the internal core of the particles.

• Standard lipospheres, as those previously described, consist of a solid hydrophobic fat core that is composed of neutral fats like tristearin, while in the polymeric lipospheres, biodegradable polymers such as polylactide (PLD) or PCL substitute the triglycerides.

• Both types of lipospheres are thought to be stabilized by one layer of phospholipid molecules surrounded by their surface.

### Present status of Nano lipospheres

For the period of the past two decades the potential of utilizing lipid-based dispersion systems as efficient drug carriers. Special administration routes have been established by many researchers and have been frequently studied both in vitro and in vivo to develop viable products. alternatively, the attractive advantages attributed to lipid dispersion systems and huge efforts provide in research. Now, there are only a few commercially available systems based on solid fats and phospholipids such as lipospheres, PNLs, and SLN. for exampleDeximune® (Dexel Pharma Ltd.) is a PNL formulation approved by the EMEA and is commercially available today. Deximune® contains the immunosuppressive complex cyclosporine A (CyA) at a quantity of 25, 50, and 100 mg, indicate for prophylaxis of organ rejection in kidney, liver, and heart allergenic transplants in combination with corticosteroids. It is used in the treatment of chronic rejection in patients formerly treated with other immunosuppressive agents, bone marrow transplantation, and endogenous uveitis. CyA is an enormously lipophilic molecule with partial water solubility and widespread intestinal first-pass metabolism and efflux, ensuing in poor and highly variable absorption from the GI tract. The PNL formulation Deximune® contains CyA in a mixture of Polysorbate 20, Sorbitan oleate, lecithin, tricaprine, macrogol glycerol hydroxy stearate, and ethyl lactate, all accepted for clinical use. This solution, which presents self-assembling PNL, is loaded into soft gelatin capsules and is administered orally. When the substance is released into the GI milieu, a nanodispersion with a particle size of 25 nm is impulsively formed in situ. The bioavailability of CyA in the product Deximune is similar to the commercial product Sandimmune Neoral® (Novartis), which forms a microemulsion in the stomach, and is up to 50% greater than that of the original Sandimmune® formulation composed of oil and alcohol solution of the drug **(25) (26) .** Achievable mechanisms responsible for the increased bioavailability of CyA PNL are inhibition of the intra-enterocyte P-GP efflux pumps and intra-enterocyte metabolism by CYP 3A enzymes.

## CURRENT & FUTURE DEVELOPMENTS

Lipospheres-based drug delivery system is an additional approach for oral, parenteral, and topical drug delivery due to their improved drug adsorption, bioavailability, and penetration properties. In addition, lipospheres are easy to manufacture in the industry in large-scale batches with minimum expenses. They can entrap the lipophilic drugs at high levels and show continuous release over a prolonged period. Also, these can successfully overcome the various problems linked with oral delivery of other drugs that suffer from poor solubility and permeability, have instability in the GIT, and undergo widespread first-pass metabolism**(27).**.Nanolipospheres-mediated oral delivery not only enhances the bioavailability of drugs entrapped into the protective lipid or fat matrix but also reduces their toxicity with coupled improvement in stability under the antagonistic environment of GIT. moreover, ease of large-scale production, avoidance of organic solvents during preparation, and use of biocompatible excipients make drug-loaded lipospheres highly amenable tocommercialization.

## NANOTECHNOLOGY IN INDIA

In India, nanoscience and technology progress has primarily been a government lead proposal. Several government departments and agencies, such as the DST, DBT, DIT, CSIR, ICMR, DAE, DRDO, and MNRE, have been supporting nanoscience and technology in different spheres and capacities. Recently launched Nanoscience and technology aims to

develop applications that serve sectors like health, water, and agriculture. Indeed public-funded projects have been instrumental in developing nanomaterial-based water filters (IIT Chennai, ARCI) as well as diagnostic kits for tuberculosis (CSIO) and typhoid (DRDO and IISc). IIT Bombay as a Centre of Excellence in nanotechnology has developed the ideas biochip that can early detect a heart attack. The Agharkar institute is also budding a therapeutic nano-silver product that has antimicrobial activity and for which clinical trials are being considered(17). The University of Delhi, the Department of Chemistry has paid alertness to rise nanoparticle encapsulation on behalf of steroidal drug delivery for ocular applications. DST, the nodal department for organizing, coordinating, and promoting S&T activities in India is the chief agency engaged in the development of nanoscience and nanotechnology. For control of the program, the Nanoscience and Technology Mission (NSTM) was established to grow India as a key player in nanoscience and technology. While it will guide this initiative between the years 2007-2012 it also hosted the flagship program, the Nanoscience andTechnology Initiative (NSTI) that was lead the way in2001 until 2006 Public sector R&D institutions play the main role in nanotechnology R&D The, 'Centers of Excellence (CoE) for Nanoscience and Technology' established under the NSTI by DST.. whereas seven "Centers for nanotechnology" also initiated that could focus on R&D in specific dimensions such as nanoelectronics (IIT Bombay) or nanoscale phenomena in biological systems and materials (Tata Institute of Fundamental Research-TIFR). The "Centers" seeks to undertake R&D to develop specific applications in a fixed period. Another "Center for Computational Materials Science" has also been established. The S.N. Bose National Centre for Basic Sciences (SN Bose NCBS), Association for the Cultivation of Science (IACS), the Indian Institute of Science (IISc), Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), and IIT Kanpur, each host a Unit of Nanoscience as well as Centre for Nanotechnology**(16).**

## CONCLUSION

Nanotechnology has probable application in many sectors including paints and coatings, textiles and clothing, cosmetics, food science, catalysis, etc.Additionally, nanotechnology presents new opportunities to improve how we measure, monitor, and manage. Nanotechnology has emerged as a growing and rapidly changing field. A new generation of nonmaterials will grow and with them new and probably unexpected issues. Nanotechnology is the prospect of advanced development. It is everything today from clothes to food there is every sector in its range we should promote it more for our expectations and more developments in our current life.

## REFERENCES


1. Bhattacharya Sujit, Bhati M,. Jayanthi, et al, 2011 . A.P.Knowledge creation and transformation process in a frontier technology: Case study of nanotechnology research in India. Advances in Nanotechnology, 7. https://niscpr.res.in/includes/images/projectreports/Nanotechnology%20Research%20and%20Innovation_0.pdf
2. Jeremy J. Ramsden (2005),"What is Nanotechnology",Collegium Basilea",[Online]Available:http://pages.unibas.ch/colbas/ntp/N03RA05.pdf
3. fileadmin/projekt/sprachen/sprachenpreis/erfolgreiche_beitraege_2007/3._Preis_07_Nanotechnology_-_Sarkis_Cattien.pdf https://projekt.bhtberlin.de/fileadmin/projekt/sprachen/sprachenpreis/erfolgreiche_beitraege_2007/3._Preis_07_-_Nanotechnology_-_Sarkis_Cattien.pdf
4. Frank Simonis & Steven Schilthuizen.Nanotechnology innovation opportunities for tomorrow'sdefence. https://books.google.co.in/books/about/Nanotechnology.html?id=ILYWSQAACAAJ&redir_esc=y
5. Domb AJ, Manier M,1990. Lipospheres for controlled delivery of pharmaceuticals, pesticides, fertilizer. Nova Pharmaceutical Corporation. 90-US6519(9107171),79,pages-8-11.https://patents.google.com/patent/CA2068216A1/un
6. Satheeshbabu N, Gowthamarajan K, 2011. manufacturing techniques of lipospheres. Int J Pharm Pharm Sci 3(4),pages- 1-11.https://www.researchgate.net/publication/288131686_Manufacturing_techniques_of_lipospheres_Overview
7. Najuma Anzar F, Prof. Dr.Mathan S and Prof. Dr. Shaju S Dharan ,et al,2020.Lipospheres . Pharm. Sci. & Res. Vol. 12(10), pages- 1357-1359 https://www.jpsr.pharmainfo.in/Documents/Volumes/vol12issue10/jpsr12102020.pdf
8. Pouton C,2006. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 29,pages- 278-87 https://www.sciencedirect.com/science/article/abs/pii/S0928098706001151
9. Nancy Dixit*, Avinash Gupta, Rajesh Asija and Manish Sharma,et al,2017. Liposphere: a noval approach of drug delivery. wjpmr, 2017,3(6),pages- 124-130. https://www.wjpmr.com/download/article/23062017/1498811099.pdf
10. Domb AJ. Ed. by Simon Benita,2006.Microencapsulation: methods and industrial applications. Lipospheres for controlled delivery of substances. Drugs and the Pharmaceutical Sciences. 2nd ed. Vol-158, CRC Press: Taylor and Francis Group; pages297-316 file:///C:/Users/HPPC/Downloads/MicroencapsulationMethodsandIndustrialApplications2ndedt.pdf
11. Cortesi R, Esposjto E, Luca G, Nastruzzi C,et al,2002. Production of lipospheres as carriers for bioactive compounds. Biomaterials; 23, pages -2283-94. https://pubmed.ncbi.nlm.nih.gov/12013175/
12. El-Gibaly I, Abdel-Ghaffar SK, 2005 Effect of hexacosanol on the characteristics of novel sustained-release allopurinol solid lipospheres (SLS): factorial design application and product evaluation. Int J Pharm ,294 pages- 33-51. https://pubmed.ncbi.nlm.nih.gov/15814229/
13. Zimmermann E, Muller RH,2001 Electrolyte- and pH-stabilities of aqueous solid lipid nanoparticle (SLN) dispersions in artificial gastrointestinal media. Eur J Pharm Biopharm 52, pages- 203-10. https://pubmed.ncbi.nlm.nih.gov/11522487/
14. Muller RH, Radtke M, Wissing SA,et al ,2002. Solid lipidnanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 54, Suppl 1: S1 pages-31-55. https://pubmed.ncbi.nlm.nih.gov/12460720/
15. Jadhav SV, Sadgir DP, Patil MP, Jagtap,et al,2014. RM, Liposphere review: methods and its applications in bio-compatible drug delivery system. World J Pharm Pharm Sci 3(9),pages-1023-43. https://www.wjpps.com/Wjpps_controller/abstract_id/2008
16. Prof. Vijaykumar. G. Tile, H.S. Suraj, B.M. Uday and S.G. Sahana et al,2016.Recent Trends in Nanotechnology and its Future Scope -A Review.International Journal on Emerging Technologies (Special Issue on ICRIET-2016) **7**(2),pages-377-385
17. Elgar A, Cherniakov I, Aldouby Y, Domb AJ, Hoffman A,et al,2012. Lipospheres and pro nano lipospheres for delivery of poorly water soluble compounds. Chem Phys Lipids 165, pages-438-53. https://pubmed.ncbi.nlm.nih.gov/22342324/#:~:text=Lipospheres%20are%20a%20drug%20encapsulation,molecules%20embedded%20in%20their%20surface**.**
18. Chinaeke EE, Chime SA, Ogbonna JDN, Attama AA, ller- Goymann CCM, Okore VC,et al,2014.Evaluation of dika waxsoybean oil-based artesunate-loaded lipospheres: *in vitro–invivo* correlation studies. J Microencapsul 31(8),pages- 796-804. https://pubmed.ncbi.nlm.nih.gov/25090593/

19. MuÈller RH, MaÈder K, Gohla S. et al,2000. Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. Eur J Pharm Biopharm, 50(1). Pages-161-177. https://pubmed.ncbi.nlm.nih.gov/10840199/
20. Sateesh Babu N ,2013. formulation design and *in vitro* evaluation of azithromycin loaded lipospheres using melt dispersion technique. journal of pharmacy research, 4(11), pages-4069-407. https://www.researchgate.net/publication/251876323_Formulation_design_and_invitro_evaluation_of_azithromycin_loaded_lipospheres_using_melt_dispersion_technique_azithromucin_lipospheres
21. Upendra CG, Umesh MB, Pravin DC, et al, 2015.Formulation Development, Optimization and In-vitro Evaluation of Glimepiride Lipospheres. Int. J. Pharm. Sci, 34(2),pages- 157-162. https://www.researchgate.net/publication/291057439_Formulation_development_optimization_and_In-vitro_evaluation_of_glimepiride_lipospheres
22. Avi Avramoff, Wahid Khan, Aviva Ezra, Anna Elgart, Amnon Hoffman, Abraham J. Domb,et al,2012. Cyclosporin pro-dispersion liposphere formulation. Journal of Controlled Release, 160,pages- 401–406. https://pubmed.ncbi.nlm.nih.gov/22227025/
23. Maha Nasr, Samar Mansour, Nahed D. Mortada, A. A. El Shamy ,etal,2008.Lipospheres as Carriers for Topical Delivery of Aceclofenac: Preparation, Characterization and In Vivo Evaluation. AAPS PharmSciTech,9(1) ,pages-154-162. https://pubmed.ncbi.nlm.nih.gov/18446476/
24. Mueller, E.A., Kovarik, J.M., van Bree, J.B., Grevel, J., Lucker, P.W., Kutz, K.,et al, 1994.Influence of a fat-rich meal on the pharmacokinetics of a new oral formulationof cyclosporine in a crossover comparison with the market formulation. Pharm.Res. 11, pages-151–155. https://pubmed.ncbi.nlm.nih.gov/8140046/
25. Bekerman, T., Golenser, J., Domb, A.,et al,2004. Cyclosporin nanoparticulate Lipospheres for oral administration. J. Pharm. Sci. 93,pages-1264–1270. https://pubmed.ncbi.nlm.nih.gov/15067702/
26. Suryakanta Swain, Sarwar Beg, Prafulla K. Sahu, Sitty M. Babu,Swaponjit Panda, Mahfoozur Rahman,et al,2016.Nanolipospheres for Oral Bioavailability Enhancement: Recent Advancements, Current Challenges and Future Directions.Current Nanomedicine, 6, pages- 69-76. http://www.eurekaselect.com/article/68108
27. 27 Khopade A.J., Jain N.K.,1997 Long circulating liposphere targeted to inflamed tissue. Pharmazie. 52: pages-165 – 166. https://pubmed.ncbi.nlm.nih.gov/9122278/
28. 28 Mohammed N, Bhise K. et.al ,2013.Formulation and development of fenofibrate loaded liposphere, Journal of Drug Delivery & Therapeutics, 3(1): pages-1-10. http://jddtonline.info/index.php/jddt/article/view/325