NANO SPANLASTICS; A NEW FORMULATION APPROACH IN NOVEL DRUG DELIVERY SYSTEM

K.Ashwin Kumar[1], S.Sathyanarayanan[2], J Gomathi[3]

[1,2] PG Scholar, [3]Assistant Professor
Department of Pharmaceutics,
C. L. Baid Metha College of Pharmacy, Tamil Nadu, India.

Abstract:In recent years researchers focused on the novel drug delivery. Because, the conventional dosage forms are not suitable for the drugs which are low solubility, low bioavailability and low permeability. To overcome those problems scientists focused on novel drug therapies. Various formulations are discovered such as, liposomes, niosomes, nanoparticles, etc., but these formulation also has some drawback such as flexibility or deformability. So researchers discovered some new system such as spanlastics released in 2011. Which has less side effects. They are elastic in nature and entrap drug in the core. Nanospanlastics are named because the vesicles of the spanlastics are nanosized and deliver the drug at targeted site and increase the bioavailability of low solubility drug which are stable than other formulations like liposomes, niosomes, nanoparticles. In this review the classification, preparation methods, mechanism, evaluation and application are highlighte

Keywords: Nanospanlastics,sliposomes,niosomes

INTRODUCTION:

In Last few decades, the researchers attention has been focused on the development of Novel Drug delivery system (NDDS)[1]. Some of the Conventional carriers are having a nature of non- flexible [2]. Hence, recent research focused to improve the Nano vesicles deformability in order to increase the permeability on biological membranes [3]. Spanlastics introduced in the year 2011. The combination of [span+elastic] is pronounced as spanlastics. Kakkar and kaur was first formulated the surfactant based deformable nano carriers.[4]

Spanlastics consists of Non-ionic surfactant and edge activators E.A. which act as a destabilizing factor of Nano carriers vesicular membranes which increases the flexibility and permeability through various biological membranes without causing any rupture.[5-6] Nano-Spanlastics are chemically more stable than liposomes and they are bio -degradable, Non-immunogenic and consists of deformable Nano-vesicles [7] The nano vesicles carrier called nano spanlastics.

Nano-Spanlastics increases its stability by encapsulating the lipophilic drug in the nano carriers and improve its permeability through the narrow pores of biological membranes due to their deformability nature, they will easily squeezed. [8-9]. This type of nano-vesicular carriers to deliver the drug at particular site and which are intended to use in various routes such as oral, Nasal, transdermal, opthalmic application.[10]

ADVANTAGES: [11-12]

- Nano-Spanlastics are biodegradable in nature.
- Nano-Spanlastics increases the bioavailability compare to the conventional form.
- Spanlastics releases the drug at Target site without causing any damages to the cell membranes and pores.
- Non ionic surfactant present in structure of spanlastics which lend them some high comparability with the biological systems.
- The bilayer which present on the spanlastics acts as a protective shield at the biological environment
- In the spanlastics system allowing the drugs which are hydrophilic or lipophilic passes through the biological membrane such as the skin,oral, topical or parentral.
- Compared to niosomes, liposomes nanospanlastics are chemically stable and induce increased bioavailability.
- Compared to other formulation nano spanlastics are economical
- Presence of Non-ionic surfactant on the vesicles they are less toxicity.

CLASSIFICATION OF NANO- SPANLASTICS

Similar to liposomes nano-spanlastics fig 1. Illustrate the classification into three types based on the number and size of vesicles which is composed which are derived as follows

1. Multi lamellar vesicles [MLV]
2. Large unilamellar vesicles [LUV]
3. Small unilamellar vesicles [SUV]
4.

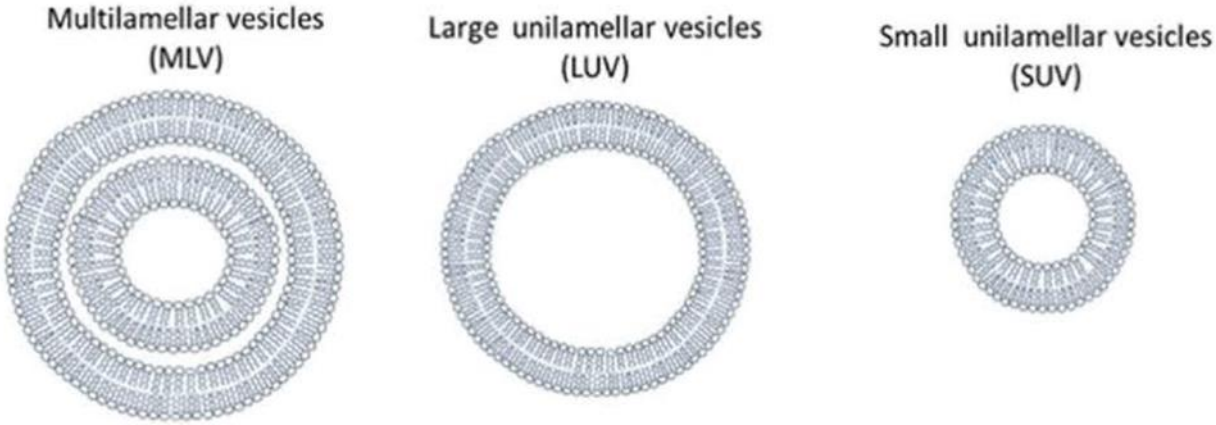

Fig.1. Classification of Nano-Spanlastics

MULTI LAMELLAR VESICLES [MLV]

In the structure of Multi lamellar vesicles [MLV] Containing number of bilayers. The approximate MLVs size is ranges from 0.5 to 1.0 micro diameter. On storage it remains stable for long period and easy to prepare.

LARGE UNILAMELLAR VESICLES [LUV]

LUV contains only one bilayer because MLV contains more bilayers. The size ranges between 100 nm to 1µm. This LUV containing a high aqueous/lipid component ratio.this ratio helps to entraps a large amount of drugs inside the core.

SMALL UNILAMELLAR VESICLES [SUV]

Similar to LUV it contains only one bilayer vesicle, But smaller in size. The size ranges from 20nm to 50 µm. SUV is prepared from MLV by various methods such as sonication method, French method, extrusion method.

STRUCTURE OF NANO-SPANLASTICS [14]

Nano-spanlastics are spherical in shape which are made up of both lipophilic and hydrophilic molecules such as hydrophilic head and lipophilic tails which serves as an encapsulation matrices.

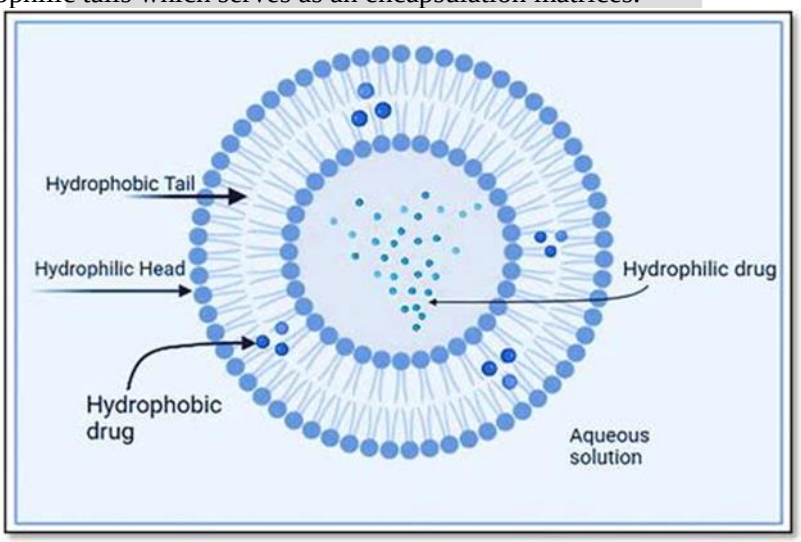

Fig.2. Structure of Nano-Spanlastics

Fig.2. illustrate that Spanlastics consists of concentric bilayers, That can be either Uni-lamellar or Multi Lamellar depends on the number of vesicles present on the core.

Depending on the size of the vesicles, these can be classified as (SUV) small unilamellar vesicles[10-100nm] and Large unilamellar vesicles (LUV)[100-300nm].

COMPONENTS OF NANO-SPANLASTICS [15]

Spanlastics are made up of essential components such as Non ionic surfactant and Edge Activators (E.A). Since the vesicles are mostly composes of surfactant so it's called as spanlastics

NON-IONIC SURFACTANT

Non ionic surfactant which forms concentric Bilayer vesicle on the aqueous based on the nature By applying some energy for instance like agitation, shaking they form concentric Bilayer structure they are arranged in a segments of hydrophilic head and hydrophilic tail [16]

In spanlastics the Non-ionic surfactant such as sorbitan alkyl esters which is refers as spans.spans arranges themselves as concentric bilayers to enhance longevity needs to incorporate saturated alkyl chain in span -60. [17]

EDGE ACTIVATORS

Surfactants like tween 80, poly vinyl alcohol (PVA) having the capacity to act as edge activators. When an hydrophilic wetting agents like PVA having a chance to injure the vesicles but increase their deformability

When EA combined with spans reduces the interfacial tension allows the spanlastics to pass through the small pores.

ETHANOL [18]

Ethanol helps to make the vesicle membrane thin, which is used to enhance the entrapment of drug more efficiently. Overall the formulation becomes stablized.

MECHANISM OF SPANLASTICS PENETRATIONS [19]:

In this current study proposing that the mechanism of spanlastics vesicles penetration into the deeper layers by two mechanism

1. The vesicles of nano spanlastics are get squeezed themselves through the small pores after penetration they will become remains intact.
2. Now spanlastics acts as a penetration enhancers by disrupting the inter cellular lipids on the biological membranes gets deeply penetrated.

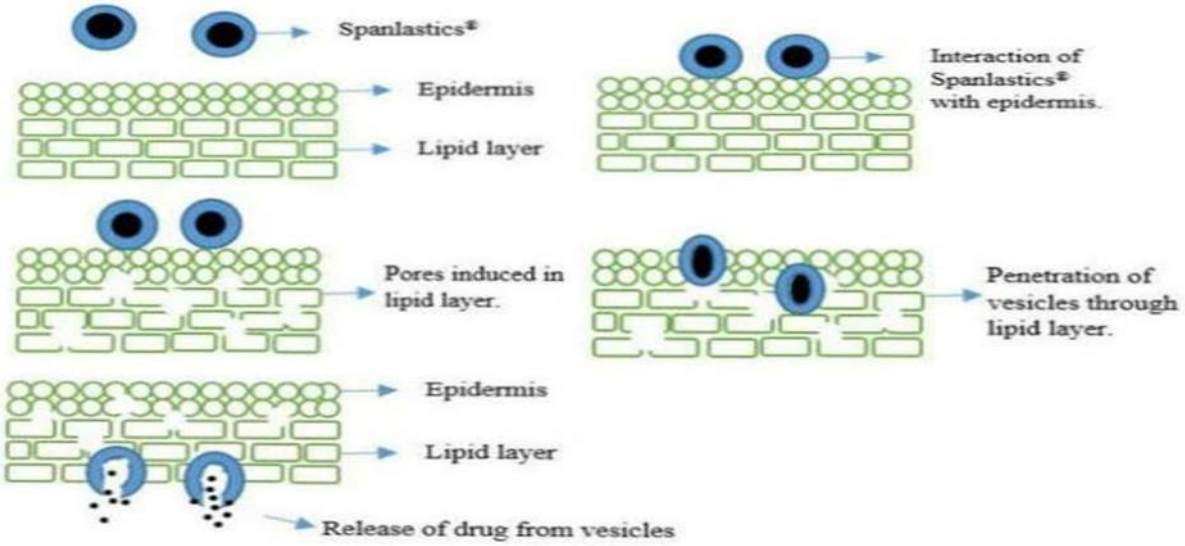

Fig.3.Mechanism of penetration of Nano-Spanlastics

Fig.3 illustrate the Mechanism of penetration of spanlastics system inside the epidermis and lipid bilayer.

1. Which represents spanlastics and organ layers
2. Interaction between the epidermis and spanlastic.
3. Penetration of vesicles through the lipid layer.

4. Releasing the drugs from the spanlastic inside the organ

So the drug which are entrapped inside the vesicles are come out and interact directly with the infected part.

METHOD OF PREPARATION:

ETHANOL INJECTION METHOD

The drug encapsulated spanlastics were prepared by Ethanol injection method.[20] A precise amount of Non ionic surfactant and drug is dissolved in ethanol. [21] fig.4.(a) illustrate the preparation of Nano spanlastics using Ethanol injection method.

The dissolved drug is coupled with span then the solution is kept under sonication for five minutes. After five minutes the solution is injected into the preheated aqueous solution which contains edge activators such as tween 80 and the solution is agitated at 800rpm–1600rpm. Kept on magnetic stirrer for another 30 minutes at 70°c-80°c [22].

ETHER INJECTION METHOD

In this method the Non-ionic surfactant is dissolved in 20 ml of ether. [23] The ethereal solution is injected into a aqueous phase which contains edge activators and maintained at 60°c. Using a 18 gauge Needle the ethereal solution is injected at the rate of 0.25 ml per minute in to the aqueous phase [24]

Once the organic solvents evaporated it will produce Single layered vesicle. As per USP ether is regarded as safe solvent and which is used for formulation development [25]

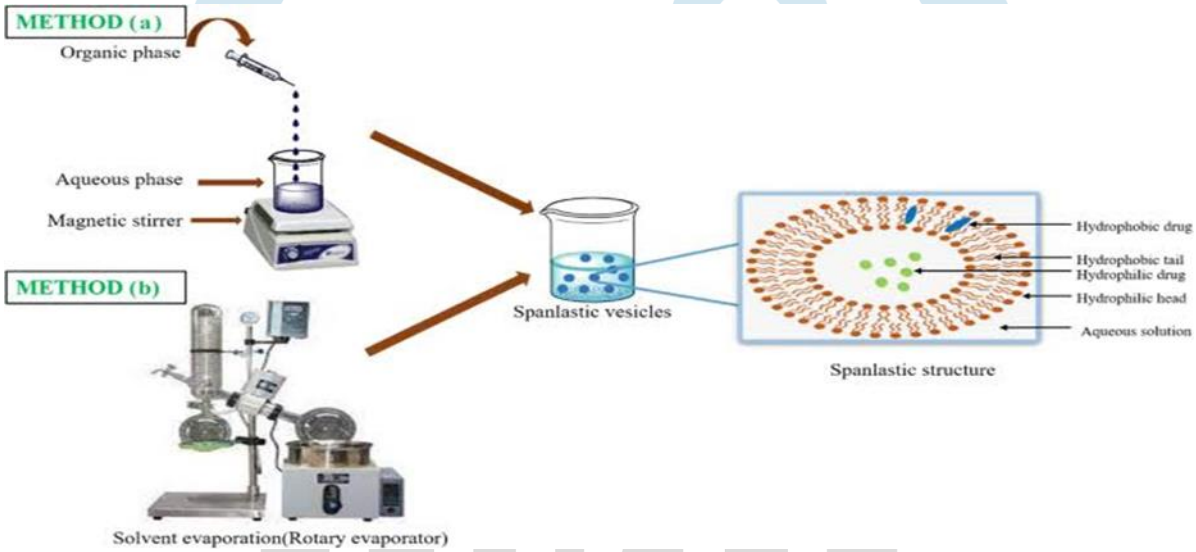

Fig.4.(a) Ethanol injection method (b) Thin film hydration method

THIN FILM-HYDRATION TECHNIQUE

Its an easy method for producing thin films in this method wetting agents such as span 60 weighed precisely in the round bottom flask that has been dissolved in the organic solvents such as chloroform which are form a thin coating on the walls of the flasks. Fig.4.(b) illustrate the preparation of Nano spanlastics using thin film hydration method.

The organic solvents are evaporated at 60°c using rotary evaporator at 90-100rpm. Then add the aqueous phase which contains the edge activators .continuous to normal rotation for 30 minutes at 90rpm the solvents gets vapourised and the film is removed from the walls. [27].

During the addition of a aqueous phase on the film Hydrophilic drugs can be added to aqueous solution although lipophilic drugs added to organic layers [28]

SONICATION [29]

In this method the spanlastics are prepared by surfactant combination and the medication are mixed in a 10ml vial.

An appropriate buffer is used to make the medication sample.using a probe whis is made up of titanium used to sonicate the mixture.

HAND SHAKING METHOD [30]

In the organic solvents such as ether or chloroform the surfactants are initially dissolved. The organic solvents which are evaporated at low vapour pressure and vaccum pressure inside the round bottom flask.After evaporation the film

gets rehydrated using an aqueous drug solution is stirred slightly.Then the vesicles traps the medication and the surfactant layer gets thicken.

EXTRUSION METHOD [31]

In the extrusion method primarily forming a thin layer using a spinning vaccum evaporator to evaporate a mixture of diacetyl phosphate and surfactantExtrude the mixture through a poly carbonate membrane with 0.1 micron pores. The membrane contains both the combined drug and rehydrated drug solution.To ensure consistency, repeating the extrusion process for 5-8 times consecutively.

MODIFIED SPRAYING TECHNIQUE

Drug loaded spanlastics vesicles are prepared by using MST [32-33] . In this method the organic phase such as non ionic surfactant are dissolved in ethanol which is transferred in to the spray device.

The aqueous phase and E.A. which are heated on the closed system at 60°c and preparing a sucrose solution. Then the organic phase is sprayed on the aqueous phase is being stirred at 1000rpm at 60°c.

The solution is sprayed at a rate of 250µl per 5S. At the end of the process the vesicles which are processed to freeze thaw cycle [34].

SPANLASTICS CHARACTERIZATION

The invitro and invivo quality control test are needed for the nano spanlastics such as

SPANLASTICS MORPHOLOGY:

The Transmission Electron Microscope (TES) is a used to identify the morphological analysis such as size, shape, lamellarity, homogeneity and physical stability the samples were analysed at an accelerated voltage of 120Kv [35]

VESICLES SIZE AND POLY DISPERSITY INDEX (PDI)

The size of vesicles and polydisperity index of the formulation is possible to measure by using dynamic light scattering [36].

ZETA POTENTIAL [37]

Zeta potential ZP is indicate the stability of colloidal dispersion. When ZP value exist between 30 mv. The system is stable due to sufficient amount of repulsive force present between particles [37]

The zeta potential of the formulation can be measured by using zeta sizer equipment [38].

NUMBER OF VESICLES IN CUBIC mm:

Using the hemocytometer to count the number of vesicles per cubic mm. Were the vesicles are appropriately diluted in water.the vesicles which having the size. So the tiny squares are counted.[39]

ENTRAPMENT EFFICIENCY [40-41]

The entrapment efficiency of the formulation such as spanlastics can be determined by using centrifugal method. The samples which are filled in 10 ml vial and kept in centrifuge for 30 minutes at 17,000 rpm.

Then take 1ml of the supernatant liquid the volume is made up of suitable solvent using UV spectrophotometry the amount of drugs present in the samples can be measured

SPANLASTICS ELASTICITY: [42]

Elasticity is termed as deformability index the elasticity of nano spanlastics can be determined by using the extrusion process using a poly carbonate filter membrane consists of 200 nm pore width used to determine the elasticity extruded for 10 minutes at a constant pressure.

$$\text{Deformability index (DI)} = J[rv/rp]2\times100$$

DIFFERENTIAL SCANNING CALORIMETRY (DSC) [43]

To determine the samples thermal property DSC is used. In this process A precise amount of sample is carefully weighed such as 5-10 mg in the closed crucible.The temperature ranges from-20°c to 150°c heating rates 100°c/min under the atmosphere of nitrogen.The resulting thermograms developed by new peaks

INVITRO STUDIES [44]

Using Franz diffusion cell the drug release can be determined in which consists of donor and receptor compartment which was separated by cellophane barrier
In the receptor compartment the ph buffer solution 6.8 is placed and the samples were placed on the dialysis membrane Maintenance of temperature at 37°c and magnetically stirred at 500rpm.at different time interval the samples which are withdrawn and analysed through uv spectroscopy to determine the % release of drugs after proper dilution.

STABILITY [45]
The non spanlastics formulation was under tested for stability by being kept in a glass vial at 4°c for 3 months
At different days interval such as 30,60&90 days of storage withdrawn and check the stability such as size, drug release were assessed.

APPLICATION OF NANO-SPANLASTICS
Originally developed for the cosmetics industry, nano-vesicles are currently gaining popularity as a vesicle medication delivery technology. because of the way that they trap both hydrophobic (lipophobic) and hydrophilic (lipophilic) substances. Spanlastics may be the best medicine delivery mechanism available. A system of nano-vesicles has already been developed for a variety of medications, including doxorubicin, vaccinations, insulin, siRNA, and many more. These vesicles can also be utilised as a co-delivery system because it is simple to load two distinct types of medication into them to provide the intended therapeutic effects. From the perspective of formulation, these vesicles have minimal toxicity, biodegradability, high stability, affordability, and convenience of storage.
Because these nanovesicles are smaller and have increased permeability, different alterations of them can also be employed to treat cancer. And the length of retention in tumour tissue.
They are easily administered by a number of channels, including As trans dermally, orally, and intravenously. Afterwards Are some instances in which the delivery of drugs by nanovascular

OCULAR DELIVERY [46-48]
The ocular medication delivery system encounters a number of challenges that restrict ocular bioavailability because of the several pre-corneal and corneal barriers. Site-specific drugs are delivered by a special kind of vesicular carriers called spanlastics. distribution methods for medications meant for the posterior part of the eye, which houses the choroid, the vitreous cavity, the epithelium, and the the anterior part of the eye, which includes the corneal membrane as well as watery humour. In addition to lipophilic It is possible to give hydrophilic medications to the eyes. tissues with elastic bands.

ORAL DELIVERY [49-51]
Although oral medicine administration is the most common method, Drugs' bioavailability can be problematic for a Many factors, such as poor solubility, frequent Dosage, medication interactions, erratic absorption, First-pass metabolism and adverse systemic reactions. To Overcome the challenges associated with oral medication delivery, a A novel vesicular system based on surfactants was Produced. Utilising spanlastic dispersions coated in enteric
For example, to encapsulate sodium pravastatin, Enables for accurate distribution and controlled release. To the stomach. Comparing it with an aqueous Medication solution, it enhanced the medication's oral Bioavailability.

TRANSDERMAL DELIVERY: [52-55]
The transdermal When administering medication, spanlastics are used. It possesses a Many advantages, such as preventing hepatic Metabolism, increasing the material's bioavailability and Medication efficiency. Delivery of medications by transdermal application Is used to create a continuous release of the medication.

NASAL DELIVERY: [56- 58]
One approach is the intranasal pathway, which proceeds straight from the From the nasal cavity to the central nervous system Trigeminal pathway following blood-brain barrier passage Going across the olfactory barrier (BBB) Area. One way to obtain medication through the BBB and enters the brain to complete a certain task The method of action is spanlastic dispersion.

TOPICAL DELIVERY: [59]
Utilised is the spanlastic system To provide medications for topical skin therapy Ailments such inflammation, fungal infections, And so forth.

PEPTIDES AND PROTEIN DELIVERY: [60-61]
Proteins and Peptides such as insulin and bacitracin, have significant therapeutic pursuits but few practical uses because of its unstable nature and limited bioavailability during administration as well as following storage. To prevent The

nano-vesicular system has demonstrated that this issue to be a superior option. Additionally, these formulae additionally aid in the vaccination process. for instance, investigated the pharmacokinetic characteristics of the insulin formulation in nanovesicles via oral administration given to diabetic rats. The information of the medication was assessed using a simulated intestinal fluid (SGF) and gastric simulated fluid (SIF). The Findings indicated that the composition had grown. bioavailability as well as resistance to deterioration.

VACCINE DELIVERY: [62]

Although vaccine development is a potent tool for treating a variety of illnesses, its use is constrained by issues with safety and effectiveness. As Consequently, nanovesicles based on non-ionic surfactants formulation may assist in preventing this deterioration.

GENE THERAPY:

As a contemporary method, while extremely effective, has limited clinical applications as a result of the delivery issue. But as of late The method of using nanovesicles is being tested.in order to modify the formulas. As an illustration, Encoding of DNA

MISCELLANEOUS :

Research investigations were conducted. out for several sodium applications the discovery of stibogluconate nano-vesicles, which be successful in combating the parasite in the spleen, liver, and bone marrow in contrast to the remedy for stibogluconate sodium.

CONCLUSION:

In the development of nano spanlastics which offers a non-invasive Technique. In this technique doesn't need any repeated administration this kind of delivery system produce a break through in the modern pharma field because in pharma field there are so much of drugs which having the problems such as low solubility, low permeability various other problems to overcome these drawbacks can be done by Nano vesicular drug delivery technology. Currently this kind of methods are administering through various delivery like Nasal, oral, Middle ear, and transungual and skin routes

REFERENCES

1. Jadhav SM, Morey P, Karpe MM et al. Novel vesicular system: an over-view. J Appl Pharm Sci 2012; 2: 193–202.
2. Badria, F.; Mazyed, E. Formulation of Nanospanlastics as a Promising Approach for Improving the Topical Delivery of a Natural Leukotriene Inhibitor (3- Acetyl-11-Keto-β-Boswellic Acid): Statistical Optimization, in vitro Characterization, and ex vivo Permeation Study. Drug Des. Dev. Ther. 2020, 14, 3697. [CrossRef]
3. Al-Mahallawi, A.M.; Khowessah, O.M.; Shoukri, R.A. Enhanced non invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles: Fabrication, in-vitro characterization, and comparative ex-vivo permeation studies.Int. J. Pharm. 2017, 522, 157–164. [CrossRef]
4. Kakkar, S.; Kaur, I.P. Spanlastics—A novel Nano vesicular carrier system for ocular delivery. Int. J. Pharm. 2011, 413, 202–210. [CrossRef]
5. Al-Mahallawi, A.M.; Khowessah, O.M.; Shoukri, R.A. Enhanced non invasive trans-tympanic delivery of ciprofloxacin through encapsulation into nano-spanlastic vesicles: Fabrication, in-vitro characterization, and comparative ex-vivo permeation studies.Int. J. Pharm. 2017, 522, 157–164. [CrossRef]
6. Zheng, W.-S.; Fang, X.-Q.; Wang, L.-l.; Zhang, Y.-J. Preparation and quality assessment of itraconazole transfersomes. Int. J. Pharm. 2012, 436, 291–298. [CrossRef] [PubMed]
7. Kamboj, S.; Saini, V.; Magon, N.; Bala, S.; Jhawat, V. Vesicular drug delivery systems: A novel approach for drug targeting. Brain 2013, 1, 11.
8. Badria, F.; Mazyed, E. Formulation of Nanospanlastics as a Promising Approach for Improving the Topical Delivery of a Natural Leukotriene Inhibitor (3- Acetyl-11-Keto-β-Boswellic Acid): Statistical Optimization, in vitro Characterization, and ex vivo Permeation Study. Drug Des. Dev. Ther. 2020, 14, 3697. [CrossRef]
9. Badria, F.; Fayed, H.A.; Ibraheem, A.K.; Mazyed, E.A. Formulation of Sodium Valproate Nanospanlastics as a Promising Approach For Drug Repurposing in the Treatment of Androgenic Alopecia. Pharmaceutics 2020, 12, 866. [CrossRef] [PubMed]
10. Mosallam S, Albash R, Abdelbari MA. Advanced Vesicular Systems For Antifungal Drug Delivery. AAPS Pharm Sci Tech, 2022; 23: 1-11.
11. Gayatri Devi S, Venkatesh P and Udupa N: Niosomal sumatriptan succinate for nasal administration. Int Journal of Pharmaceutical Science 2000; 62: 479-81.
12. Vindhya V.S, Krishnananda kamath.k., Sandeep Kumar Jain and Shabaraya A.R, Spanlastics: A Modern Formulation Approach in Drug Delivery 2023,10(4), 96-102.

13. Imam S S. The Future of Non-Invasive Ways to Treat Cancer .Int J Pharm Scie Res, 2021; 12(9): 4684-96.
14. Sharma A, Pahwa S, Bhati S, Kudeshia P.Spanlastics: A Modern Approach For Nanovesicular Drug Delivery System. Int J Pharma Sci Res, 2020; 11(3): 1057-65
15. VS V, Kamath K, Jain SK, AR S. SPANLASTICS: A MODERN FORMULATION APPROACH IN DRUG DELIVERY.
16. Diljyot K. Niosomes: a new approach to targeted drug delivery. Int J Pharm Phytopharm Res. 2012; 2:53–9.
17. Sahil singh, Manpreet Kaur Walia, Pryanka, Anuradha Kumari:Spanlastic advanced approach as nanovesicular drug delivery system.2023;ISSN: 2455-2631
18. Alhammid, Shaimaa N. Abd; Kassab, Hanan J.; Hussein, Lina S.; Haiss, Mahmood A.; and Alkufi, Hussein k. (2023) "Spanlastics Nanovesicles: An Emerging and Innovative Approach for Drug Delivery," Maaen Journal for Medical Sciences: Vol. 2 : Iss. 3 , Article 2.
19. Sallam N, Sanad R, Khafagy E S, Mahgoub A, Ghourab M, Gad Shaded. Colloidal Delivery of Drugs Present Strategies and Conditions. Rec Pharm Biomed Sci, 2021; 5(3): 40-51.
20. Badria, F.; Mazyed, E. Formulation of nanospanlastics as a promising approach for improving the topical delivery of a natural leukotriene inhibitor (3- Acetyl-11-Keto-β-Boswellic Acid): Statistical optimization, in vitro characterization, and ex vivo permeation study. Drug Des. Dev. Ther. 2020, 14, 3697. [CrossRef]
21. Elsaied EH, Dawaba HM, Ibrahim ESA, Afouna MI. Effect ofpegylated edge activator on span 60 based-nanovesicles:comparison between Myrj 52 and Myrj 59. Univers. J. Pharm. Res. 2019;4(4):1e8. https://doi.org/10.22270/ujpr.v4i4.290.
22. Aml I, Mekkawy AI, Nermin E, Eleraky, Ghareb M, Soliman, Mohamed G, Elnaggar G Et Al. Combinatorial Therapy Of Letrozole- And Quercetin-Loaded Spanlastics For Enhanced Cytotoxicity Against MCF-7 Breast Cancer Cells Pharmaceutics, 2022; 14: 2-21.
23. Kaur IP, Rana C, Singh M, Bhushan S, Singh H,Kakkar S. Development And Evaluation Of Novel Surfactant-Based Elastic Vesicular System For Ocular Delivery Of Fluconazole. J Ocular Pharma, 2012; 1-13.
24. Ballie, A.J. The preparation and properties of niosomes- non-ionic surfactant vesicles. J. Pharm. Pharmacol. 37:863–868, 1985.
25. United States Pharmacopeia National Formulary (USP NF-29) Residual Solvents. In: U.S. Pharmacopeia. 2009; p. 171–182. United State Pharmacopeial Convention, Maryland, USA.
26. El Menshawe SF, Nafady MM, Aboud HM, Kharshoum RM, Elkelawy AMMH, Hamad DS. Transdermal delivery of fluvastatin sodium via tailored spanlastic nanovesicles: miti-gated Freund's adjuvant-induced rheumatoid arthritis in rats through suppressing p38 MAPK signaling pathway. Drug Deliv 2019;26(1):1140e54. https://doi.org/10.1080/10717544.2019.1686087.
27. Farghaly DA, Aboelwafa AA, Hamza MY, Mohamed MI. Topical Delivery Of Fenoprofen Calcium Via Elastic Nano-Vesicular Spanlastics: Optimization Using Experimental Design And In Vivo Evaluation. AAPS Pharm Sci Tech, 2017; 8:1-6.
28. Gaafar PME, Abdallah OY, Farid RM, Abdelkader H. Preparation, characterization and evaluation of novel elastic nanosized niosomes (ethoniosomes) for ocular delivery of prednisolone. J Liposome Res 2014;24(3):204e15. https://doi.org/10.3109/08982104.2014.881850.
29. Alisagar S, Tushar KV, Mansoor MA. Nanocarriers for systemic and mucosal vaccine delivery. Recent Pat Drug Delivery Formulation 2007;1(1):1e91. https://doi.org/10.2174/187221107779814140.
30. Lee VH, Robinson JR. Enzymatic Barriers to Peptide and Protein Absorption. Crit Rev Ther Drug Carrier Syst 1998;5(2):69e97. PMID: 3052875.
31. Alleman E, Leroux JC, Gurny R. Polymeric Nano-and Microparticles for the oral delivery of peptides and peptidomimetics. Adv Drug Deliv Rev 1998;34(2e3):171e89. https://doi.org/10.1016/s0169-409x(98)00039-8.
32. Refaat H, Naguib YW, Elsayed MM, Sarhan HA, Alaaeldin E.Modified spraying technique and response surface methodology for the preparation and optimization of propolis liposomes of enhanced anti-proliferative activity against human melanoma cell line A375. Pharmaceutics.
2019;11(11). https://doi.org/10.3390/pharmaceutics11110558
33. Alaaeldin E, Mostafa M, Mansour HF, Soliman GM. Spanlastics as an efficient delivery system for the enhancement of thymoquinone anticancer efficacy: fabrication and cytotoxic studies against breast cancer cell lines. J Drug Deliv Sci Technol.2021;65: 102725. https://doi.org/10.1016/j.jddst.2021.102725.
34. Ali MM, Shoukri RA, Yousry C. Thin Film Hydration Versus Modified Spraying Technique to Fabricate Intranasal Spanlastic Nanovesicles For Rasagiline Mesylate Brain Delivery: Characterization, Statistical Optimization, And in Vivo Pharmacokinetic Evaluation. Drug Delivery and Translational Research, 2022; 1-16.
35. Aliaa N, Elmeshad, Mohsen AM. Enhanced Corneal Permeation and Antimycotic Activity of Itraconazole Against Candida Albicans Via A Novel Nano system Vesicle. Drug Deliv, 2016; 23(7): 2115–123.
36. Kakkar S, Kaur IP. Spanlastics A novel nanovesicular carrier system for ocular delivery. International journal of pharmaceutics. 2011 Jul 15;413(1-2):202-10.

37. Abdelbary AA, Abd-Elsalam WH, Al-mahallawi AM. Fabrication of novel ultradeformable bilosomes for enhanced ocular delivery of terconazole: in vitro characterization, ex vivo permeation and in vivo safety assessment. Int J Pharm. 2016;513(1–2):688–696.doi:10.1016/j.ijpharm.2016.10.006
38. Abdelbari MA, El-Mancyss, Elshafeeyah,Abdelbaryaa. Implementing Spanlastics For Improving the Ocular Delivery of Clotrimazole: In Vitro Characterization, Ex Vivo Permeability, Microbiological Assessment And In Vivo Safety Study Int J Nanomedicine, 2021; 16: 6249–6261
39. Mohanta P, Narendra K. Pandey NK, Kapoor DN,.Singh SK, Sarvi Y, Sharma P. Development of Surfactant-Based Nanocarrier System for Delivery of An Antifungal Drug. J Pharm Res, 2017; 11(9):1153-158.
40. Alharbi WS, Hareeri R H, Bazuhair M, Alfaleh M A, Alhakamy N A, Fahmy U an Et Al .Spanlastics As A Potential Platform for Enhancing the Brain Delivery of Flibanserin: In Vitro Response-Surface Optimization And In Vivo Pharmacokinetics Assessment. Pharmaceutics, 2022; 14(2627): 1-16.
41. Saleh A, Khalifa M, Shawky S, Bani-Ali A, Eassa H. Zolmitriptan Intranasal Spanlastics For Enhanced Migraine Treatment; Formulation Parameters Optimized Via Quality by Design Approach. Sci. Pharm, 2021; 89(24): 1-10.
42. Sallam NM, Abdel R, Sanad B, Ahmed MM, Khafagy EL, Ghorab M, Gad S. Impact of The Mucoadhesive Lyophilized Wafer Loaded with Novel Carvedilol NanoSpanlastics On Biochemical Markers in The Heart of Spontaneously Hypertensive Rat Models. Drug Deliv. And Transl.Res, 2020; 1-30.
43. Abbasa H, Kamel R. Potential Role of Resveratrol-Loaded Elastic Sorbitan Monostearate Nanovesicles For the Prevention Of UV-Induced Skin Damage. J LIPOSOME RES, 2020; 30(1): 45–53.
44. Yassin Ge, Reham I. Amer, Ahmed M, Fayez. Carbamazepine Loaded Vesicular Structures for Enhanced Brain Targeting Via Intranasal Route:Optimization, In Vitro Evaluation, And In Vivo Study. Int J App Pharm, 2019; 11(4): 264-74.
45. Shahira F. El Menshawe, Mohamed M. Nafady, Heba M. Aboud, Rasha M. Kharshoum, Asmaa Mohammed M. Hussein Elkelawy & Doaa S. Hamad Transdermal Delivery of Fluvastatin Sodium Via Tailored Spanlastic Nanovesicles: Mitigated Freund's Adjuvant Induced Rheumatoid Arthritis in Rats Through Suppressing P38 MAPK Signaling Pathway, Drug Delivery, 2019; 26(1): 1140-154.
46. Lian T, Ho RJY. Trends and developments in liposome drug delivery systems. J Pharm Sci 2001; 90: 667–680. Crossref. PubMed. ISI.
47. Sharma A, Shilpa Pahwa S , Savita Bhati S , P Kudeshia . Formulation and Evaluation of Dorzolamide Spanlastics. Int J Pharm Sci Res, 2020;11(8): 3930-35.
48. Cortesi R, Argnani R, Esposito E, et al. Cationic liposomes as potential carrier for ocular administration of peptides with anti-herpetic activity. Int J Pharm 2006; 317: 90–100. Crossref. PubMed.
49. Gregoriadis G, Florence AT. Liposomes in drug delivery. Clin, Diagn Ophthalmic Potential Drugs 1993;45:15–28.
50. Gregoriadis G. Fate of injected liposomes: observations on entrapped solute retention, vesicle clearance and tissue distribution in vitro. In:Gregoriadis G, editor. Liposomes as drug carriers: recent trends and progress. New York: Plenum Press; 1988. p. 3–18.
51. Badr Eldin S M, Aldawsari H M, Alhakamy N A, Fahmy U A, Ahmed O A A, Neamatallah T, Tima S, Almaghrabi R H, Alkudsi F M, Alamoudi A Aetal. Merging Experimental Design and Nanotechnology for The Development of Optimized Simvastatin Spanlastics: A Promising Combined Strategy for Augmenting the Suppression of Various Human Cancer Cells. Pharmaceutics, 2022; 14(1024): 1-10
52. Lund W. in Pharmaceutical codex. 1994; Pharmaceutical press: London. p.
134-159.
53. Rolland A. Particulate carriers in dermal and transdermal drug delivery: myth or reality, in Pharmaceutical Particulate Carriers:Therapeutic applications., Hadgraft J. Editor. Marcel Dekker: New York. 1993; 367-421.
54. Barry BW. Lipid-Protein-Partitioning theory of skin penetration enhancement: J Control Release 1991; 15(3): 237-248.
55. Fahmya AM, El-Setouhyada, Ahmed B, Ibrahim, Basant A. Habiba Etal. Penetration Enhancer-Containing Spanlastics (Pecss) For Transdermal Delivery of Haloperidol: In Vitro Characterization,Ex Vivo Permeation and In Vivo Biodistribution Studies. Drug Delivery, 2018; 25(1): 12–22.
56. Hinchcliffe, M.; Illum, L. Adv. Drug Del. Rev., 1999, 35(2-3), 199-234.
57. Hussain, A.A. Adv. Drug Del. Rev., 1998, 29(1-2), 39-49.
58. Abdelmonema R, Nabarawib M, Attiaa A.Development of Novel Bioadhesive Granisetron Hydrochloride Spanlastic Gel and Insert for Brain Targeting and Study Their Effects on Rats Drug Delivery, 2018; 25(1): 70-77.
59. Elhabaka M, Ibrahimb S Samar M. Abouelatta. Topical Delivery Of L-Ascorbic Acid Spanlastics For Stability Enhancement and Treatment of UVB Induced Damaged Skin. Drug Delivery, 2021; 28(1): 445-53.
60. Gupta P.N., Mishra V., Ranat A., Dubey P., Mahor S., Jain S., Chatterji D.P. andVyas S.P., Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: A comparative study, Int. J.Pharm., 2005; 293: 73-82.

61. Manosroi A, Jantrawut P, Khositsuntiwong N,Manosroi W, Manosroi J. Novel Elastic Nanovesicles For Cosmeceutical and Pharmaceutical Applications. Chiang Mai J Sci, 2009; 36(2): 168-78.
62. Ali M M, Shoukri RA, Yousry C. Thin film hydration versus modified spraying technique to fabricate intranasal spanlastic nanovasicles for rosagiline mesylate brain delivery:characterization,statistical optimization and in-vivo pharmacokinetic evaluation. Drug Deliv Trans Res, 2022; 1-16.