

**SPANLASTICS: A MODERN FORMULATION APPROACH IN DRUG DELIVERY**

Vindhya V. S.\*, Krishnananda Kamath K., Sandeep Kumar Jain and Shabaraya A. R.

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Farangipete post, Mangalore, Karnataka, India  
– 574143.**\*Corresponding Author: Vindhya V. S.**

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Farangipete post, Mangalore, Karnataka, India – 574143.

Article Received on 23/01/2023

Article Revised on 13/02/2023

Article Accepted on 3/03/2023

**ABSTRACT**

In the field of nanotechnology, novel vesicular drug delivery systems have advanced significantly. These systems are valuable in evading various drawbacks associated with conventional dosage forms, like low aqueous solubility, poor bioavailability, poor membrane permeability, variable plasma concentration, undesirable effects, poor patient compliance, and poor patient efficacy. Thus, with the advent of novel drug delivery systems such as liposomes, nanoemulsions, nanosuspensions, and nanoparticles, these are proving to be a better option nowadays. A new system called Spanlastics, which has fewer side effects, was released in 2011 as part of the progression of drug delivery. They are a novel elastic vesicular drug delivery system based on surfactants that trap the drug in the core cavity in the form of a bilayer. Which are amphiphilic in nature, the drug is contained within a vesicle comprised of a non-ionic surfactant. They have been found to be more stable chemically. They provide medicinal ingredients with targeted delivery and regulated release, and they have overcome a number of problems with the traditional dosage form. The classification of spanlastics, the mechanism of penetration, various preparation techniques, evaluation factors, and applications are highlighted in the current review.

**KEYWORDS:** Nanotechnology, Membrane permeability, Spanlastics, Surfactants.**INTRODUCTION**

Vesicular drug delivery is one of the best approaches for therapeutic administration of pharmaceutical compounds. These systems have been widely employed for a number of objectives, such as drug targeting, controlled release, and permeation enhancement of drugs. They have the potential to carry a variety of drugs, such as lipophilic and hydrophilic drugs. Spanlastics are a novel vesicular drug delivery system that entraps the drug in the core cavity in the form of a bilayer. The term Spanlastic (Span + Elastic) was first used in 2011. These elastic carriers are deformable. In comparison with a drug solution, these deformable vesicular carrier systems exhibit enhanced permeability.<sup>[1]</sup> Spanlastics are extremely tiny and microscopic in size. These have an amphiphilic character, where the drug is contained in a vesicle formed by a non-ionic surfactant. These vesicles elastic properties are a result of the structure's inclusion of edge activators. These nanovesicles outperform liposomes in areas where they lack, such as chemical instability. Due to their propensity for oxidative breakdown and varying phospholipid purity, liposomes are chemically unstable. This special class of vesicular carriers serves as site-specific drug delivery systems for medications that are intended for use in ophthalmic, oral, topical, nasal, and transungual applications.<sup>[2]</sup>

**Advantages<sup>[3]</sup>**

- Spanlastics are non-immunogenic and biodegradable by nature.
- Increased Bioavailability: Because the medication has protected support, it reaches the targeted site without being shredded off, increasing bioavailability in comparison to the conventional one.
- The spanlastics system allows hydrophilic or lipophilic drugs to pass through biological membranes such as the cornea.
- By encapsulating the medicine inside a lipid bilayer structure, they shield it from the biological environment.
- They improve the therapeutic execution of medicated particles by shielding the medication from the environment and limiting the impact on the targeted site.
- They boost the stability of the medicine that has been entrapped and are osmotically active and stable.
- They play an important role in delaying the clearance of drug molecules from the systemic circulation during sustained drug delivery.
- The presence of non-ionic surfactants in their structures lends them high compatibility with biological systems and imparts low toxicity.

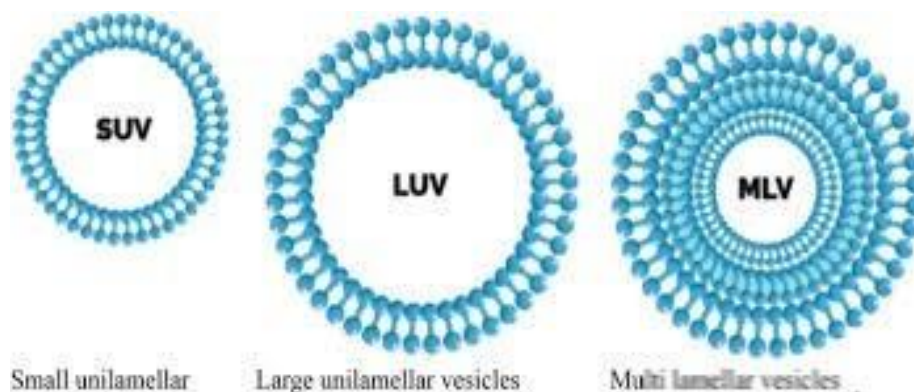
- Handling and storage of surfactants require no special conditions.
- They can be made to reach the site of action by oral, parenteral, or topical routes.

#### Classification of spanlastic<sup>[4]</sup>

It is classified on the basis of numbers of layer it composes of, which is illustrated as follows

- Multi-Lamellar Vesicles (MLV): MLVs structure consists of a number of the bilayer.
- The approx. size of MLVs is 0.5 to 1.0-micron diameter.

- It is commonly used, easy to make and remains stable upon storage for a long period.
- ii. Large Unilamellar Vesicles (LUV): The size range of LUVs is between 100 nm and 1  $\mu$ m.
- LUVs have a high aqueous/ lipid component ratio and this ratio helps it to entrap a larger amount of drug inside the core.
- iii. Small Unilamellar Vesicles (SUV): The size of SUVs is generally in the range of 20 nm to 50  $\mu$ m.
- SUVs are prepared from multi-lamellar vesicles by the sonication method.

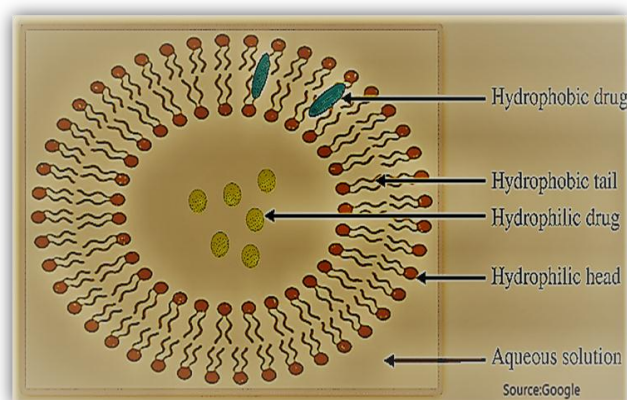


**Fig. 1: Classification of spanlastic.**

#### Structure and Composition<sup>[5]</sup>

Spanlastics systems are spherical structures made up of amphiphilic molecules that serve as bioencapsulation matrices. It consist of concentric bilayers, these can be Unilamellar or Multilamellar depending on the size of vesicles, these can be (SUVs) Small unilamellar (10-100 nm) or (LUVs) Large unilamellar (100-3000 nm).

Spanlastics are made up of a nonionic surfactant and an Edge activator, which are both essential components. Since these vesicles are primarily composed of surfactants, they have been named Spanlastics.



**Fig 2: Structure of spanlastic.**

**Non ionic surfactants:** Surface-active substances, also known as surfactants, work to reduce the interfacial tension between two liquids. A charged group does not exist in the head of a non-ionic surfactant. An essential class of non-ionic surfactants is composed of sorbitan alkyl esters (Spans). In order to create the vesicular structure of spanlastic, spans form concentric bilayers. The polyoxyethylene sorbitan component of the

molecule, known as the span, comes in various types, including Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate). The stability of the vesicular formulation can be predicted in large part by looking at the types of Span. Vesicles based on Span 80 and Span 40 exhibit significant disruption, aggregation, and instability. In

contrast, the inclusion of saturated alkyl chains in Span 60 increases its sustainability.

**Edge activators:** These are a unique type of surfactant with high hydrophilicity, or the HLB value. These surfactants only have one chain. Edge activators are components that soften the bilayer, such as biocompatible surfactants, to which an amphiphilic substance is added to increase the permeability and flexibility of the lipid bilayer. It increases the deformability of the bilayer by lowering the interfacial tension between them. EAs have a propensity to produce larger spherical vesicles, which results in smaller particle sizes. Tween 80 is an edge activator that makes vesicles more elastic. Any vesicle larger than the pore size of the biological membrane can easily transfer from the outside to the inside as a result of the tween-80's temporary increase in pore size.

Additionally, this promotes greater drug penetration and the transfer of larger amounts of drugs inside the vesicle. These hydrophilic surfactants can also destabilise vesicular membranes, make them more deformable, and create systems with different degrees of disruption in packing characteristics.

**Ethanol:** The characteristics of these nanovesicular carriers are improved by ethanol. Its capacity to

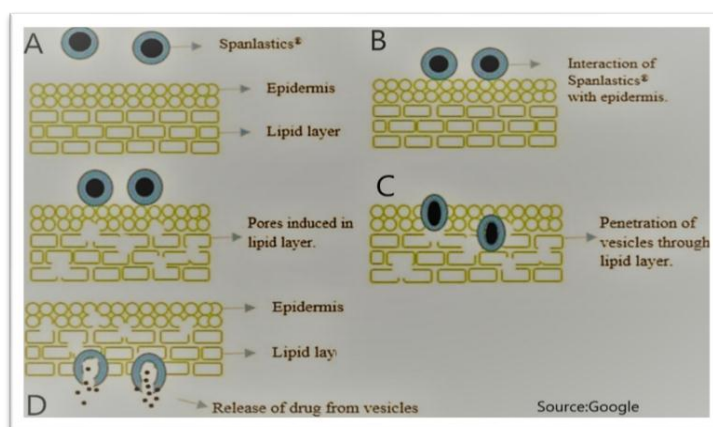
condense membranes makes it useful. It aids in enhancing drug entrapment and partitioning within the vesicles. The vesicular membrane's thickness is reduced, and the spanlastic system's ability to entrap drugs is enhanced. Additionally, by changing the system's net charge toward a negative zeta potential, it stabilises the steric effect to some extent.

#### Mechanism of penetration<sup>[6]</sup>

There are two methods by which drugs penetrate the body. The intercellular lipid lamellae are altered as a result of the elastic vesicles' interactions and penetration-enhancing functions with the epithelial cell membrane. The elastic vesicles can function as drug-carrier systems, allowing intact vesicles containing the drug to breach the biological membrane and flow across intercellular spaces.

The following elements aid in these carriers' effective passage:

- The vesicle bilayers' extremely stress-dependent flexibility
- The existence of an osmotic gradient
- In the higher concentration range, the surfactant causes a solubilization (lysis).
- Edge activators (EAs) weaken the lipid bilayers, which makes the vesicles more deformable.



**Fig. 3: Mechanism of penetration of spanlastic system inside the Epidermis and Lipid layer.**

- The figure A represents the spanlastic and the layers of the organ.
- In the figure, B we can see the interaction between the spanlastic system and the epidermis and the formation of pores inside the layers of the organ.
- The figure C represents the penetration of the spanlastic system through the layers.
- The figure D represents the release of drugs from the spanlastic system inside the organ.

Due to this, the drug entrapped inside the system comes directly in contact with the infected part.

#### Method of preparation

- **Ether injection:**<sup>[7]</sup> This method involves slowly injecting surfactant in 20 ml of ether using a 14-

gauze needle at a rate of 25 ml per minute into a 4 ml aqueous phase that has been heated to 600 oC. Using a rotary evaporator, the ether solution will be evaporated. Once the organic solvent has evaporated, it will produce single-layered vesicles.

- **Ethanol injection method:**<sup>[8]</sup> This technique can be used to create spanlastics with a set ratio of non-ionic surfactant to edge activator. The medicine to be encapsulated is dissolved in ethanol coupled with span. Five minutes are spent sonicating the lipid solution. Now, this solution is continuously injected into a heated aqueous phase containing an edge activator (such as Tween-80), which has been agitated at 800-1600 rpm and 70–80°C for 30 minutes on a magnetic stirrer. Another 30 minutes

are spent stirring the mixture at a cool temperature. With distilled water, the final formulation is adjusted to 10 ml.

- **Thin film hydration technique:**<sup>[9]</sup> Span 60 that has been precisely weighed will be placed to a flask with a circular bottom and dissolved in chloroform. A thin coating will form on the flask walls as the organic solvent is evaporated at 55°C under vacuum using a rotary evaporator at 90 rpm. The chosen EA and cosolvent will dissolve a specific amount of medication in the aqueous phase. The deposited thin film will get the addition of this aqueous phase. Once more secured to the evaporator, the flask will be rotated for 30 minutes at normal pressure, 60°C, and 90 rpm to completely remove the lipid film from its walls. The distribution that results will be left overnight at 4°C after standing for a further 2 hours at room temperature to hydrate completely.
- **Modified spraying technique:**<sup>[10]</sup> This method is also used to prepare spandex. This approach involves forming the organic phase, which is subsequently transferred to a spray device, by dissolving non-ionic surfactants in 2 mL ethanol. A closed system is used to heat the aqueous phase to 60 °C and prepare a sucrose solution (9% w/v in double-distilled water). The organic phase is then sprayed over the aqueous medium while being stirred at 1500 rpm and 60 °C at a rate of 250 L per 5 s. In order to improve the trapping of the medication inside the Nano system, the resulting spanlastic vesicular systems underwent four successive freeze-thaw cycles at -8 °C for 8 h and 25 °C for 1 h.

#### Characteristics of spanlastics

To access the in vitro and in vivo behaviour of the Spanlastics formulation, precise and repeatable quality control procedures are needed.

- **Morphology examination:**<sup>[11]</sup> The transmission electron microscope is used for morphological analysis to identify the lamellarity, homogeneity of size, shape, and physical stability properties of spanlastics.
- **Vesicle Size & PDI:**<sup>[12]</sup> Using the dynamic light scattering approach, the size and polydispersity index (PDI) of the formulation may be measured.
- **Zeta potential:**<sup>[13,14]</sup> Using a zeta sizer equipment, the zeta potential of the spanlastic formulation is measured. It aids in identifying the reasons behind flocculation, aggregation, or dispersion.
- **Number of vesicles per cubic millimetre:**<sup>[15]</sup> The vesicles were appropriately diluted with water, and the haemocytometer was used to count the number of vesicles per cubic mm. The vesicles in 80 tiny squares were counted, and the formula below was used to calculate the number of vesicles/mm<sup>3</sup>.
- **Efficiency of entrapment:**<sup>[16,17]</sup> Using the centrifugation method, the efficiency of entrapment

was assessed. After centrifuging a 10 ml sample of the spanlastics dispersion at 17,000 rpm for 60 min. at °C, the supernatant is recovered. A 10ml volumetric flask containing 1ml of supernatant was used, and the volume was made up using a suitable solvent. The amount of drug present in the supernatant was measured using UV spectrophotometry.

- **Measurement of elastic properties:**<sup>[18]</sup> Elasticity is represented by the deformability index (DI). Using an extrusion process, the elasticity of nano-spanlastics is determined. Using a polycarbonate membrane with a 200-nm pore width as a filtering membrane, nano-spanlastics were produced and extruded for 10 minutes at a constant vacuum pressure.

Deformability is determined using following equation:

$$\text{Deformability index (DI)} = \frac{J}{rv/rp} \times 100$$

where,

**J** is the weight of sample in grams pressed in 10 min and passed across a polycarbonate filtration membrane

**rv** is the size of spanlastic vesicles after extrusion

**rp** is the pore size of the polycarbonate membrane filter

- **Differential scanning calorimetry:**<sup>[19]</sup> Differential scanning calorimetry is used to determine a sample's thermal properties. In this investigation, a 40-L aluminium crucible is carefully weighed with a sample of 5–10 mg of the extrudate within, and the crucible is covered. The temperature range for all tests was -20 to 150 OC, with heating rates of 10 OC/min under a nitrogen atmosphere. The resulting thermograms are checked for any inconsistencies, such as large shifts or the removal or development of new peaks.

- **In vitro drug release studies:**<sup>[20]</sup> Franz diffusion cells were used in the studies on in vitro drug release. The donor compartment and the receptor compartment were separated by a cellophane barrier. With the receptor compartment filled with phosphate buffer of pH 6.8 and the weighed amount of spanlastic placed on one side of the dialysis membrane, the temperature is kept at 37°C while being magnetically swirled at 500 rpm. Samples in the acceptor chamber are removed at specified intervals and immediately placed with an identical volume of buffer. The material is analysed spectrophotometrically at max after the proper dilution.

- **Stability test:**<sup>[21]</sup> The spanlastic formulation was tested for stability by being kept in a glass vial at 4 °C for three months. Samples were taken out of the system at specified intervals of After 30, 60, and 90 days of storage, EE%, particle size, size distribution, and drug release were assessed.



### Applications

Nano-vesicles firstly emerge in the field of cosmetics and now attracting at a wide range as a vesicle drug delivery system. Due to their nature of entrapment of both hydrophilic (lipophobic) and well as hydrophobic (lipophilic) drugs. Spanlastics can be an ideal system for drug delivery. Nano-vesicles system is already designed for drugs such as doxorubicin, vaccines, insulin, siRNA and many more; having a wide variation in usage. These vesicles can also be used as a co-delivery system as two different kinds of drugs can be easily loaded to achieve the desired therapeutic effects. As a formulation point of view, these vesicles possess biocompatibility, low toxicity, biodegradability, good stability, low cost and ease of storage. Various modifications of these nano-vesicles can also be used in the treatment of cancer due to their smaller size, leading to enhanced permeability and retention time in tumour tissue.

They can be easily administered by various routes such as intravenously, orally and trans dermally. Following are some areas where this nano-vascular drug delivery system is being used:

- **Ocular delivery:**<sup>[22]</sup> Due to numerous pre-corneal and corneal barriers, the ocular drug delivery system faces a number of difficulties that limit ocular bioavailability. Spanlastics, a unique class of vesicular carriers, serve as site-specific drug delivery systems for drugs that are intended for the posterior eye segment, which contains the choroid, epithelium, and vitreous cavity, as well as the anterior eye segment, which consists of the corneal membrane and aqueous humour. Both lipophilic and hydrophilic drugs can be administered to the ocular tissues using spanlastics.
- **Oral delivery:**<sup>[23]</sup> The oral route is the most popular for administering medications, although oral medications have issues with bioavailability for a variety of reasons, including low solubility, frequent dosing, drug interactions, unpredictable absorption, first-pass metabolism, and systemic side effects. To get around the difficulties with oral drug delivery, a unique surfactant-based vesicular system was created. Using enteric-coated spanlastic dispersions, for instance, to encapsulate pravastatin sodium, allows for controlled release and precise distribution to the duodenum. When compared to an aqueous drug solution, it improved the medicine's oral bioavailability.
- **Transdermal delivery:**<sup>[24]</sup> The transdermal medication administration uses spanlastics. It has a number of benefits, including avoiding hepatic metabolism, which enhances bioavailability and drug effectiveness. Transdermal medication delivery is employed to produce a constant drug release.
- **Nasal delivery:**<sup>[25]</sup> One of the methods is the intranasal route, which travels directly from the nasal cavity to the central nervous system via the trigeminal pathway after crossing the blood-brain barrier (BBB) and passing through the olfactory

region. One method for getting medicine via the BBB and into the brain to carry out a specific activity is by means of spanlastic dispersion.

- **Topical delivery:**<sup>[26]</sup> The spanlastic system is used to deliver drugs for topical treatment of skin conditions such as fungal infections, inflammation, and so on.
- **Peptides and Proteins:**<sup>[27]</sup> Peptides and proteins such as bacitracin and insulin have important therapeutic activities but limited clinical applications due to low bioavailability and instability during administration and after storage. In order to avoid this problem, the nano-vesicular system has proven to be a better choice. Further, these formulations also contribute to the delivery of vaccines.

For example, Pardakhty studied the pharmacokinetic properties of the nanovesicular insulin formulation in diabetic rats via oral administration. The content of the drug was evaluated in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF). The results showed that the formulation has increased bioavailability and is protected from degradation.

- **Vaccines:**<sup>[28]</sup> Vaccine formulation is a powerful tool for the treatment of a number of diseases, but its use is limited due to its safety and efficacy problems. As a result, non-ionic surfactant-based nanovesicles formulation can help to avoid this degradation.
- **Gene therapy:** Gene therapy, as a modern approach, is very powerful but has limited clinical applications due to the delivery problem. But now the nanovesicular approach is being experimented with to modulate the formulations. For example, DNA encoding.
- **Miscellaneous:** Experimental studies were carried out for multiple applications of sodium stibogluconate nano-vesicles, which were found to be effective against the parasite in the liver, spleen, and bone marrow as compared to the solution of sodium stibogluconate.

### CONCLUSION

The development of Spanlastics, surfactant-based vesicles offers a non-invasive technique for drug delivery to the target site without the requirement for repeated medication administration. They address the problems of insolubility, instability, limited bioavailability, and rapid degradation of drugs. Spanlastics may represent a breakthrough in the nano vesicular drug delivery technology, it may be inferred from this. Both lipophilic and hydrophilic drugs can achieve site-specific action by utilising these vesicular systems. Currently, this technique employed to administer medication to the middle ear, nasal passages, transungual area, oral cavity, and skin.

### REFERENCES

1. Witika BA, Mweetwa LL, Tshiamo KO, Edler K, Matafwali SK, Ntemi Pvetal. Vesicular Drug

- Delivery For The Treatment Of Topical Disorders: Current And Future Perspectives. *J Pharm Pharmacology*, 2021; 73(11): 1427-41.
- Mosallam S, Albash R, Abdelbari MA. Advanced Vesicular Systems For Antifungal Drug Delivery. *AAPS Pharm Sci Tech*, 2022; 23: 1-11.
  - Verma A, Chauhan MK. Spanlastics-Future of Drug Delivery and Targeting. *W J Pharm Res*, 2017; 12(6): 429-46.
  - Imam S S. The Future of Non-Invasive Ways to Treat Cancer. *Int J Pharm Scie Res*, 2021; 12(9): 4684-96.
  - 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.
  - Sallam N, Sanad R, Khafagy E S, Mahgoub A, Ghorab M, Gad Shaded. Colloidal Delivery of Drugs Present Strategies and Conditions. *Rec Pharm Biomed Sci*, 2021; 5(3): 40-51.
  - 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 Ther*, 2012; 1-13.
  - Aml I, Mekkiy 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.
  - 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.
  - 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.
  - Aliaa N, Elmehad, 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.
  - Kakkar S, Kaur IP. Spanlastics—A Novel Nano Vesicular Carrier System for Ocular Delivery. *Int J Pharm*, 2011; 413: 202-10.
  - 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.
  - Mazyed E A, Helal D A, Elkhoudary M M, Abd Elhameed AG, Yasser M. Formulation and Optimization of Nanospanlastics For Improving the Bioavailability of Green Tea Epigallocatechin Gallate. *Pharmaceutics*, 2021; 14(68): 1-30.
  - 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.
  - 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.
  - 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.
  - 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.
  - 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.
  - Yassin Ge, Reham I. Amer, Ahmed M, Fayed. 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.
  - Shahira F. El Menshawe, Mohamed M. Nafady, Heba M. Aboud, Rasha M. Kharshoum, Asmaa Mohammed M. Hussein Elkelayy & 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.
  - 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.
  - 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
  - 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.
25. 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.
  26. Elhabaka M, Ibrahim 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.
  27. 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.
  28. Ali M M, Shoukri RA, Yousry C. Thin film hydration versus modified spraying technique to fabricate intranasal spanlastic nanovesicles for rosagiline mesylate brain delivery: characterization, statistical optimization and *in-vivo* pharmacokinetic evaluation. *Drug Deliv Trans Res*, 2022; 1-16.