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Spanelastic as a vesicular nanocarrier for transdermal drug delivery system: Preparation, characterization and bioactive loading

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ABSTRACT: Spanlastic is a novel surfactant-based elastic nanovesicle delivery system that has been shown to deliver many different types of drugs. The present review aimed to illustrate the structure, composition, evaluation and discuss some bioactive compounds that can be delivered by spanlastics. Spanlastics are composed of a non-ionic surfactant and an edge activator, which gives them their elasticity. This elasticity allows spanlastics to deform and squeeze through the skin pores, making them ideal for transdermal delivery. Spanlastics have also been shown to be effective in delivering drugs to the eye, buccal mucosa, and other tissues. Spanlastics have several advantages over other drug delivery systems. They are non-immunogenic, biodegradable, and chemically stable. They are also more elastic than liposomes, which makes them more effective at penetrating biological membranes. In addition, spanlastics can be formulated to target specific tissues, which can improve the therapeutic efficacy of the drug. Spanlastics are a promising new drug delivery system with a wide range of potential applications. They are currently being investigated for the treatment of a wide range of diseases, including cancer, inflammation, and infectious diseases. Finally, this review leads to a conclude that Spanelastic can be used as a good Vesicular Nanocarrier for transdermal drug delivery system.

KEYWORDS: Spanelastic; vesicular nanocarrier; transdermal drug delivery; olive tree; curcumin; green tea.

1. INTRODUCTION

The skin is the biggest organ of the human body, covering about 1.8 square meters of the total body surface. It serves as a barrier between the body and the external environment. The transdermal route, which involves delivering drugs through the skin, offers more advantages than the traditional routes. It is non-invasive and bypasses the liver's first-pass metabolism. This route allows for long-lasting drug concentration, reducing the frequency of dosing and improving patient compliance. Transdermal delivery is especially beneficial for patients who cannot swallow tablets or capsules, as well as for controlled-release medications that should not be crushed [1,2]. Spanlastics are a new type of elastic vesicular system, made up of sorbitan esters (known as "spans") and edge activators. Among the different types of Spans, Span 60 is widely used due to its saturated alkyl chains and lipophilic properties, which help in the development of stable single- and multi-layered lipid vesicles with high entrapment efficiency. In addition to spans, Spanlastics also contain edge activators such as tween, which increase the fluidity and the ability of the vesicles to squeeze through narrow spaces [3,4]. The spanlastics have several advantages such as biodegradable, biocompatible, less dosing frequency of medication, non-immunogenic, chemically stable, improved oral bioavailability of poor soluble medicines, and skin permeability of drug when administered topically compared to liposome [5,6]. The Spanlastics are used in oral, ocular, nasal, topical, transdermal and transungual drug delivery [7,8].

2. STRUCTURE OF SPANLASTIC

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Spanlastics are spherical structures made up of amphiphilic molecules. They are around 180-450 nanometers in diameter [9,10]. The hydrophilic drugs are incorporated in the middle of the vesicle while the hydrophobic drugs are incorporated in the tail part of the vesicle as seen in Figure 1.

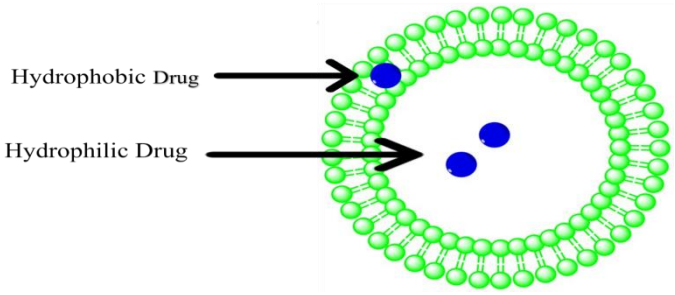

Figure 1. Structure of Spanlastic

3. COMPOSITION OF SPANLASTIC

The Spanlastics is composed of specific ingredients, namely non-ionic surfactants, edge activators, and ethanol [9] summarized in Table 1.

Table 1. Components of the Spanlastic

Component	Non-Ionic Surfactant	Edge Activator	Ethanol
Function	Improve the stability of the vesicle	Enhance Flexibility of the vesicle	Improve the permeability of the vesicle
Most commonly Used	Span 60	Tween 80	Ethanol

3.1 Non-ionic Surfactant

These are the most commonly used wetting agents in vesicle preparation due to their superior properties such as compatibility, stability, and low toxicity. They consist of polar and non-polar components, which make them highly effective at forming bilayer vesicles. The formation of these vesicles depends on various factors such as critical packing parameters, the chemical structure of the components, and the Hydrophilic–lipophilic balance (HLB) value of the wetting agent [9,10]. According to the HLB value, lower values such as those found in span 80 and span 40 results in more disruption, aggregation, and instability compared to vesicles made with span 60. This is because span 60's lipophilic nature enables the formation of more stable lamellar matrix vesicles. Additionally, span 60 is more effective at encapsulating drugs than other non-ionic surfactants. Therefore, the choice of wetting agent plays a crucial role in vesicle formation, and non-ionic surfactants such as span 60 are highly preferred due to their superior properties and ability to form stable vesicles for drug delivery applications [11].

3.2 Edge Activators

The use of an edge activator can decrease the interfacial tension of the vesicles and make them more flexible. This means that larger particles can more easily pass through the pores in the membrane. Tween-80 and PVA are examples of edge activators that can be used. Polyvinyl alcohol can also be used to reduce the size of the vesicles and increase their elasticity. However, hydrophilic wetting agents can also deteriorate the vesicular membranes which paradoxically improves their deformability [12].

3.3 Ethanol

It is a good penetration enhancer that is important in spanlastic systems. It gives the vesicles different properties, such as entrapment efficacy, stability, zeta potential, size, and increased permeability of skin. When the alcohol concentration is too high, it will make the vesicle membrane leaky. This will cause the vesicles to get slightly bigger and release more of their contents and the vesicles will completely dissolve. In addition, When the concentration of ethanol is high, the ethanol molecules are close enough together that they start to interact with each other and form a network of intertwined molecules, which reduces the thickness of the vesicular membrane and therefore the size of the vesicles. Alcohol can change the electrical charge of particles in a liquid, which can help to keep them from clumping together., which means that it

creates a barrier around the vesicles that prevents them from clumping together. Therefore, it is important to find an optimal level of alcohol to use to maintain the desired surface properties and permeability of the vesicles [13].

4. PRODUCTION AND DEVELOPMENT OF SPANLASTICS VESICLES

The Spanlastics are produced using either the methods of ethanol injection or thin-film hydration, both of which are commonly used in the industry [14-16].

4.1 Thin Film Hydration

This method is mostly used straightforward technique for preparing films. It involves dissolving wetting agents in an organic solvent within a rounded bottom flask. The rotary vacuum evaporator removes the organic solvent, leaving a thin film on the inner wall of the flask. To hydrate the film, an aqueous solution as water should be added at a temperature above the transition temperature (Tc) of the surface-active agent. If the drug is lipophilic, it should be added to the organic layer while if the drug is hydrophilic, it should be added to the aqueous solution during the hydration process of the film. This method can be used with modified spraying technique to produce vesicles that are both small and efficient at encapsulating drugs [14,15].

4.2 The Ethanol Injection

The ethanol injection method is a technique used to prepare Spanlastics, which are formulations containing a non-ionic surfactant and an edge activator in a specific ratio. In this method, a precise amount of the non-ionic surfactant and the drug are dissolved in ethanol and then injected into a heated aqueous phase. The aqueous phase contains the edge activator for the Spanlastics. The mixture is continuously stirred at a high speed and temperature for a certain period of time. Afterward, the final volume is adjusted using distilled water. However, there are some limitations associated with this technique. One drawback is the difficulty in removing residual ethanol because it forms an azeotrope (a mixture with a constant boiling point) with water. Additionally, even small amounts of ethanol present in the formulation may deactivate biologically active macromolecules, posing a risk to their effectiveness [16].

5. CHARACTERIZATION OF SPANELASTIC

The summary of the characterization and their effect on Spanlastics was illustrated in Table 2.

Table 2. Summary of the characterization and their effect on Spanlastics

The Characterestics	Effect on the vesicle
Particle size	The lower the hydrophile-lipophile balance (HLB) of the surfactant, the smaller the vesicle size - Increase the concentration of an edge activator (sodium deoxycholate), decrease the vesicle size
Zeta Potential (ZP)	Stable when the ZP value is close to ± 30mV
Polydispersity index (PDI)	Decrease the polydispersity, improve the the vesicle size
In vitro release characteristics	Constant release of the drug
Entrapment Efficiency	Increasing Entrapment Efficiency, improve the formulation
TEM	vesicles were spherical in shape with a well-defined sealed structure

5.1 Particle size, Zeta Potential (ZP), and Polydispersity index (PDI)

The average particle size and polydispersity index (PDI) of drug-loaded vesicles is determined using dynamic light scattering (DLS) (Zetasizer Nano). The sample is diluted with distilled water before measurement and repeated three times [17,18]**.** The value of PDI is always between 0 and 1. Low PDI values indicate uniformity in the particle size distribution and a monodisperse population but a higher PDI indicates more heterogeneity [19].

The more polydisperse the vesicle size distribution is, the less regular the size of the vesicle in the formulation. [20] In general, the system is usually stable when the ZP value is close to ± 30mV because the particles in the system repel each other electrically [21]. When the hydrocarbon tail of a surfactant is longer, the vesicles formed are larger in size. Because Span 60 has the longest hydrocarbon tail without any double bonds, it forms the largest vesicles [22]. Shahira F. El Menshawe *et al* investigated fluvastatin-loaded

spanelastic vesicles (SNVs) and found that the average size of SNVs made with Span 60 (HLB 4.7) was larger than those made with Span 80 (HLB 4.3). The authors hypothesizes that the lower the hydrophile-lipophile balance (HLB) of the surfactant, the smaller the vesicle size produced. Therefore, SNVs made with Span 80 (HLB 4.3) are smaller in diameter than those made with Span 60 (HLB 4.7)[9]. Increasing hydrophobicity reduces surface energy, which leads to the formation of smaller vesicles, could be attributed to the association between the surfactant HLB and vesicle size that was found [22]. The concentration of edge activator has a significant on the particle size, Shamma *et al* found that large amount of edge activator caused a significant decrease in the particle size [23]. Dora *et al.* found similar results during the study of preparation of glibenclamide nanoparticles at higher particle size concentrations. They found that lower surface tension, which is caused by higher particle size concentrations, makes it easier for the particles to divide and form smaller nanovesicles [24]. Another study found the formation of significantly smaller spanlastics vesicles when the concentration of sodium deoxycholate increasing as an edge activator [25].

5.2 *In vitro* release characteristics

By using modified Franz diffusion cells (Franz diffusion cell with dialysis membrane) an exact volume of each formulation is placed in the donor cell, and the dialysis process is performed. A specific milliliter sample was withdrawn at each time interval and replaced with equal volumes of the liquid medium. Then amount of the drug in each sample is measured spectrophotometrically. The way that a drug is released from spanlastic formulations is affected by the attractive forces between the phospholipids in the bilayer, which slows down the release of the drug [26].

5.3. Entrapment Efficiency

This test is carried out to separate the vesicles from the unentrapped or free drug by using the ultracentrifugation method. The Spanlastics formulation is centrifuged. The clear supernatant (free drug) is separated and filtered with a nylon syringe filter and the precipitate is washed with Phosphate Buffered Saline (PBS) and then assayed using a UV spectrophotometer. The drug entrapment efficiency is expressed as a percentage (EE %) and calculated as the equation below [9]:

EE% = {(total drug concentration – free drug concentration) / Total drug concentration } X 100

5.4. Elasticity Measurement:

The elasticity of a spanelastic membrane was tested by passing a suspension of vesicles through filters of cellulose acetate filters at a definite pressure with the help of an air compressor. The measurements of elasticity are compared by using an equation that expresses the elasticity of the vesicles in terms of a deformability index (DI).

$DI = J (r_v/r_p)^2$

The deformability index (DI) is equal to the weight of dispersion extruded in 10 minutes (J) multiplied by the square of the ratio of the size of vesicles after extrusion (nm) (r_v) to pore size of the barrier (nm) (r_p) [27].

5.5. *Ex* Vivo Permeation Study

This test involves using an animal according to the Ethics guidelines. The hair of the abdominal skin of the rat is carefully removed by shaving and their abdominal skin is collected. The skin is divided by scissors into pieces of proper size. Within period of time of collection, the excised shaved abdominal skin of mice is thawed and used to study the *ex vivo* permeation of the drug from the prepared spanlastic formulations [28].

5.6. Morphological Studies

The morphologic test is a microscopy technique used to examine the structural features of vesicles, such as their size, shape, lamellarity, and aggregation. To perform the test, a drop of diluted vesicle dispersion is placed on a specific grid and allowed to settle. The excess fluid is removed with filter paper, and at room temperature, the grid is left to dry. The grid is then examined under a transmission electron microscope (TEM). The TEM image provides information about the size, shape, and lamellarity of the vesicles. The size of the vesicles can be measured directly from the image. The shape of the vesicles can be described as spherical, elliptical, tubular, or other shapes. The lamellarity of the vesicles can be determined by the number of concentric bilayers in the vesicle membrane. The TEM image can also be used to detect the presence of aggregated vesicles. Aggregated vesicles are groups of two or more vesicles that are stuck

together. Aggregated vesicles can be caused by a variety of factors, such as high vesicle concentration, pH, and ionic strength. Overall, the morphologic test is a valuable tool for assessing the quality and purity of vesicle dispersions [29,30].

6. BIOACTIVE

6.1. Olive Tree

Olive trees are an important part of Mediterranean culture, and they have been cultivated for thousands of years. Over 300 varieties of olive trees have been developed to produce different types of olive oil and other products. Olive trees are relatively low-maintenance and can live for hundreds of years. Olive fruits and leaves have been used in traditional medicine for many centuries [31]. Studies have shown that olive oil can reduce blood sugar levels, cholesterol levels, and uric acid levels. Olive oil can also be used to treat diabetes, high blood pressure, inflammatory diseases, diarrhea, respiratory tract infections, urinary tract infections, intestinal diseases, and hemorrhoids [32, 33]. Olive leaves contain a number of phenolic compounds, including iridoids and secoiridoids. These compounds have been the focus of much research in recent years, and they have been shown to have a variety of pharmacological properties. Olive fruits are edible and contain a number of beneficial phenolic compounds. Volatile compounds from olive fruits and leaves have also been studied extensively, and they have been shown to play a role in the flavor and aroma of olive oil [34]. Many naturally active components have a wide range of therapeutic effects, but their use is limited by their low stability under different pH and temperature conditions, their hydrophobicity, and their bitter taste. To address these limitations, researchers have developed advanced delivery systems, such as nanocarriers, to promote the bioavailability and therapeutic potential of these components. One example of such a delivery system is the liposome of O. europaea extract. This liposome formulation was shown to enhance the stability of the extract components [31–34]. Alnusaire *et al.*, 2021 [35] formulated a spanlastic formulation of Olea europaea leaves and showed a promise approach.

6.2. Curcumin

Turmeric, a plant related to ginger, originated in India and is now grown worldwide. It is a popular spice in Indian and Asian cuisine, adding both flavor and color. India is the leading producer and exporter of turmeric [36,37]. Curcumin, a compound found in turmeric, has been the subject of much research in recent years due to its potential therapeutic benefits, including anti-inflammatory, anti-diabetic, anti-cancer, and anti-aging properties. These findings are supported by evidence from laboratory, animal, and human studies [38,39]. Ismail et al., 2023 [40] formulated a spanlastic of curcumin. The spanlastics were able to increase the number of apoptotic cells, which confirms that they are a promising new delivery system for melanoma treatment.

6.3 Green Tea

Natural plants are a valuable and affordable source of drugs that can be used to treat a variety of diseases. Green tea, obtained from the leaves of the tea plant (Camellia sinensis), is a popular traditional health drink and a good source of antioxidant polyphenols. However, black tea loses these beneficial effects due to the oxidation of its chemical components [41–43]. Catechins are the main polyphenolic compounds in green tea and are responsible for most of its antioxidant effects. Many studies have attributed the various health benefits of green tea to epigallocatechin gallate (EGCG), the most important green tea flavonoid [44,45]. EGCG has attracted the attention of many researchers as a promising drug in the pharmaceutical, nutritional, and cosmetic fields. It has exhibited many pharmacological activities, including anti-tumor, antioxidant, and anti-inflammatory effects. It also has beneficial effects on cardiovascular diseases, diabetes, Parkinson's disease, stroke, Alzheimer's disease, and obesity [46]. However, EGCG has limited bioavailability, meaning that only a small amount of it is absorbed into the bloodstream and reaches its target tissues. This limits its pharmacological applications and accounts for the significant discrepancy between ex vivo and in vivo studies. The poor bioavailability of EGCG is due to its high hydrophilicity, which makes it difficult to penetrate cell membranes. Additionally, EGCG is unstable and susceptible to environmental factors such as pH changes, oxygen, and other stressors [47–49].

Encapsulating EGCG in different formulations is an effective way to address these limitations. Formulations can protect EGCG from degradation and improve its absorption into the bloodstream. Mazyed et al., 2021 [50] enacpslate Green Tea Epigallocatechin Gallate in spanlastic to increased bioavailability and enhanced pharmacological effects.

Collectively, naturally occurring bioactive compounds have the potential to treat a wide range of diseases. However, their application is limited due to chemical instability, quick degradation, low absorption, and low bioavailability [51]. These challenges are demonstrated in bioactive polyphenols, which have a wide range of health applications. Hence, extensive investigations are being conducted to encapsulate them to improve their stability and efficacy [52]. One of these approaches is the spanelastic drug delivery system.

7. CONCLUSION

Spanelastic as nano elastic vesicles have been extensively delivered for topical and transdermal medicine in various medical conditions. They have also successfully delivered therapeutic compounds to different body parts such as the skin, trans-lingual, brain, nasal, and ocular. Spanlastics with modifications have also been reported to enable better and more precise medication delivery.

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REFERENCES

[1] Ahmed Saeed Al-Japairai K, Mahmood S, Hamed Almurisi S, Reddy Venugopal J, Rebhi Hilles A, Azmana M, Raman S. Current trends in polymer microneedle for transdermal drug delivery. Int J Pharm. 2020;587:119673. https://doi.org/10.1016%2Fj.ijpharm.2020.119673

[2] Phatale V, Vaiphei KK, Jha S, Patil D, Agrawal M, Alexander A. Overcoming skin barriers through advanced transdermal drug delivery approaches. J Control Release. 2022;351:361–380. https://doi.org/10.1016/j.jconrel.2022.09.025

[3] Verma S, Utreja P. Vesicular nanocarrier based treatment of skin fungal infections: Potential and emerging trends in nanoscale pharmacotherapy. Asian J Pharm Sci.2019;14:117–129. https://doi.org/10.1016/j.ajps.2018.05.007

[4] Abdelbari MA, El-Mancy SS, Elshafeey AH, Abdelbary AA. 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. https://doi.org/10.2147/ijn.s319348

[5] Elmowafy E, El-Gogary RI, Ragai MH, Nasr M. Novel antipsoriatic fluidized spanlastic nanovesicles: In vitro physicochemical characterization, ex vivo cutaneous retention and exploratory clinical therapeutic efficacy. Int J Pharm. 2019;568:118556. https://doi.org/10.1016/j.ijpharm.2019.118556

[6] Liu Y, Wang Y, Yang J, Zhang H, Gan L. Cationized hyaluronic acid coated spanlastics for cyclosporine A ocular delivery: Prolonged ocular retention, enhanced corneal permeation and improved tear production. Int J Pharm. 2019;565:133–142. https://doi.org/10.1016/j.ijpharm.2019.05.018

[7] Lalu L, Tambe V, Pradhan D, Nayak K, Bagchi S, Maheshwari R, Kalia K, Tekade RK. Novel nanosystems for the treatment of ocular inflammation: Current paradigms and future research directions. J Control Release. 2017;268:19-39. https://doi.org/10.1016/j.jconrel.2017.07.035

[8] Abdelmonem R, El-Enin HAA, Abdelkader G, Abdel-Hakeem M. Formulation and characterization of lamotrigine nasal insert targeted brain for enhanced epilepsy treatment. Drug Deliv. 2023;30:2163321. https://doi.org/10.1080%2F10717544.2022.2163321

[9] El Menshawe SF, Nafady MM, Aboud HM, Kharshoum RM, Elkelawy AMMH, Hamad DS. 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 Deliv. 2019;26:1140–1154. https://doi.org/10.1080%2F10717544.2019.1686087

[10] Ferreira MD, Duarte J, Veiga F, Paiva-Santos AC, Pires PC. Nanosystems for brain targeting of antipsychotic drugs: An update on the most promising nanocarriers for ıncreased bioavailability and therapeutic efficacy. Pharmaceutics. 2023;15(2):678. https://doi.org/10.3390%2Fpharmaceutics15020678

[11] Ibrahim SS, Abd-Allah H. Spanlastic nanovesicles for enhanced ocular delivery of vanillic acid: design, in vitro characterization, and in vivo anti-inflammatory evaluation. Int J Pharm. 2022;625:122068. https://doi.org/10.1016/j.ijpharm.2022.122068

[12] Agha OA, Girgis GNS, El-Sokkary MMA, Soliman OAE-A. Spanlastic-laden in situ gel as a promising approach for ocular delivery of Levofloxacin: In-vitro characterization, microbiological assessment, corneal permeability and in-vivo study. Int J Pharm. 2023;6:100201. https://doi.org/10.1016/j.ijpx.2023.100201

[13] Ansari MD, Saifi Z, Pandit J, Khan I, Solanki P, Sultana Y, Aqil M. Spanlastics a novel nanovesicular carrier: Its potential application and emerging trends in therapeutic delivery. AAPS PharmSciTech. 2022;23(4):112.https://doi.org/10.1208/s12249-022-02217-9

[14] Gaafar PME, Abdallah OY, Farid RM, Abdelkader H. Preparation, characterization and evaluation of novel elastic nano-sized niosomes (ethoniosomes) for ocular delivery of prednisolone. J Liposome Res. 2014;24:204–215. https://doi.org/10.3109/08982104.2014.881850

[15] 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 Deliv Transl Res. 2023;13:1153–1168. https://doi.org/10.1007/s13346-022-01285-5

[16] Elsaied EH, Dawaba HM, Ibrahim ESA, Afouna MI. Effect of Pegylated Edge activator on Span 60 based-nanovesicles: Comparision between MYRJ 52 and MYRJ 59. Univers J Pharm Res. 2019; 4(4):1-8 https://doi.org/10.22270/ujpr.v4i4.290

[17] Mahmoud MO, Aboud HM, Hassan AH, Ali AA, Johnston TP. Transdermal delivery of atorvastatin calcium from novel nanovesicular systems using polyethylene glycol fatty acid esters: Ameliorated effect without liver toxicity in poloxamer 407-induced hyperlipidemic rats. J Control Release. 2017;254:10-22. https://doi.org/10.1016/j.jconrel.2017.03.039

[18] Fahmy AM, El-Setouhy DA, Ibrahim AB, Habib BA, Tayel SA, Bayoumi NA. Penetration enhancer-containing spanlastics (PECSs) for transdermal delivery of haloperidol: In vitro characterization, ex vivo permeation and in vivo biodistribution studies. Drug Deliv. 2018;25:12–22. https://doi.org/10.1080/10717544.2017.1410262

[19] Esquerdo VM, Dotto GL, Pinto LAA. Preparation of nanoemulsions containing unsaturated fatty acid concentrate-chitosan capsules. J Colloid Interface Sci. 2015;445:137–142. https://doi.org/10.1016/j.jcis.2014.12.094

[20] ElMeshad AN, Mohsen AM. Enhanced corneal permeation and antimycotic activity of itraconazole against *Candida albicans* via a novel nanosystem vesicle. Drug Deliv. 2016;23:2115–2123. https://doi.org/10.3109/10717544.2014.942811

[21] Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future. Adv Drug Deliv Rev. 2001;47:3–19. https://doi.org/10.1016/s0169-409x(00)00118-6

[22] Khallaf RA, Aboud HM, Sayed OM. Surface modified niosomes of olanzapine for brain targeting via nasal route; preparation, optimization, and in vivo evaluation. J Liposome Res. 2020;30:163–173. https://doi.org/10.1080/08982104.2019.1610435

[23] Shamma RN, Sayed S, Sabry NA, El-Samanoudy SI. Enhanced skin targeting of retinoic acid spanlastics: in vitro characterization and clinical evaluation in acne patients. J Liposome Res. 2019;29:283–290. https://doi.org/10.1080/08982104.2018.1552706

[24] Dora CP, Singh SK, Kumar S, Datusalia AK, Deep A. Development and characterization of nanoparticles of glibenclamide by solvent displacement method. Acta Pol Pharm. 2010;67:283–290.

[25] Elsherif NI, Shamma RN, Abdelbary G. Terbinafine hydrochloride trans-ungual delivery via nanovesicular systems: In vitro characterization and ex vivo evaluation. AAPS PharmSciTech. 2017;18:551–562. https://doi.org/10.1208/s12249-016-0528-9

[26] Mekkawy AI, Eleraky NE, Soliman GM, Elnaggar MG, Elnaggar MG. Combinatorial therapy of letrozole- and quercetin-loaded spanlastics for enhanced cytotoxicity against MCF-7 breast cancer cells. Pharmaceutics. 2022;14(8):1727. https://doi.org/10.3390/pharmaceutics14081727.

[27] Fahmy AM, El-Setouhy DA, Habib BA, Tayel SA. Enhancement of transdermal delivery of haloperidol via spanlastic dispersions: Entrapment efficiency vs. particle size. AAPS PharmSciTech. 2019;20(3):95. https://doi.org/10.1208/s12249-019-1306-2

[28] Alaaeldin E, Abou-Taleb HA, Mohamad SA, Elrehany M, Gaber SS, Mansour HF. Topical nano-vesicular spanlastics of celecoxib: Enhanced anti-inflammatory effect and down-regulation of TNF-α, NF-κB and COX-2 in complete Freund's Adjuvant-Induced Arthritis model in rats. Int J Nanomedicine. 2021;16:133–145. https://doi.org/10.2147/ijn.s289828

[29] Tayel SA, El-Nabarawi MA, Tadros MI, Abd-Elsalam WH. Duodenum-triggered delivery of pravastatin sodium via enteric surface-coated nanovesicular spanlastic dispersions: Development, characterization and pharmacokinetic assessments. Int J Pharm. 2015;483:77–88. https://doi.org/10.1016/j.ijpharm.2015.02.012

[30] Gupta I, Adin SN, Rashid MA, Alhamhoom Y, Aqil M, Mujeeb M. Spanlastics as a potential approach for enhancing the nose-to-brain delivery of piperine: In vitro prospect and ın vivo therapeutic efficacy for the management of epilepsy. Pharmaceutics. 2023;15(2):641. https://doi.org/10.3390/pharmaceutics15020641

[31] Kalua CM, Allen MS, Bedgood DR, Bishop AG, Prenzler PD, Robards K. Olive oil volatile compounds, flavour development and quality: A critical review. Food Chem. 2007;100:273–286. https://doi.org/10.1016/j.foodchem.2005.09.059

[32] El SN, Karakaya S. Olive tree (*Olea europaea*) leaves: potential beneficial effects on human health. Nutr Rev. 2009;67:632–638. https://doi.org/10.1111/j.1753-4887.2009.00248.x

[33] Kanakis P, Termentzi A, Michel T, Gikas E, Halabalaki M, Skaltsounis A-L. From olive drupes to olive oil. An HPLC-orbitrap-based qualitative and quantitative exploration of olive key metabolites. Planta Med. 2013;79:1576–1587. https://doi.org/10.1055/s-0033-1350823

[34] Hashmi MA, Khan A, Hanif M, Farooq U, Perveen S. Traditional uses, phytochemistry, and pharmacology of *Olea europaea* (Olive). Evid Based Complement Alternat Med. 2015;2015:541591. https://doi.org/10.1155%2F2015%2F541591

[35] Alnusaire TS, Sayed AM, Elmaidomy AH, Al-Sanea MM, Albogami S, Albqmi M, Alowaiesh BF, Mostafa EM, Musa A, Youssif KA, Refaat H, Othman EM, Dandekar T, Alaaeldin E, Ghoneim MM, Abdelmohsen UR. An ın vitro and ın silico study of the enhanced antiproliferative and pro-oxidant potential of *Olea europaea* L. cv. Arbosana leaf extract via elastic nanovesicles (Spanlastics). Antioxidants (Basel). 2021;10(12):1860. http://dx.doi.org/10.3390/antiox10121860

[36] Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives - A review. J Tradit Complement Med. 2016;7(2):205-233. https://doi.org/10.1016/j.jtcme.2016.05.005.

[37] Carolina Alves R, Perosa Fernandes R, Fonseca-Santos B, Damiani Victorelli F, Chorilli M. A critical review of the properties and analytical methods for the determination of curcumin in biological and pharmaceutical matrices. Crit Rev Anal Chem. 2019;49:138–149. https://doi.org/10.1080/10408347.2018.1489216

[38] Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4:807–818. https://doi.org/10.1021/mp700113r

[39] Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: Lessons learned from clinical trials. AAPS J. 2013;15(1):195-218. https://doi.org/10.1208%2Fs12248-012-9432-8

[40] Ismail S, Garhy D, Ibrahim HK. Optimization of topical curcumin spanlastics for melanoma treatment. Pharm Dev Technol. 2023;28(5):425-439. https://doi.org/10.1080/10837450.2023.2204926

[41] Ramadan G, El-Beih NM, Abd El-Ghffar EA. Modulatory effects of black v. green tea aqueous extract on hyperglycaemia, hyperlipidaemia and liver dysfunction in diabetic and obese rat models. Br J Nutr. 2009;102(11):1611-1619. https://doi.org/10.1017/s000711450999208x

[42] Rashidinejad A, Birch EJ, Sun-Waterhouse D, Everett DW. Delivery of green tea catechin and epigallocatechin gallate in liposomes incorporated into low-fat hard cheese. Food Chem. 2014;156:176–183. 10.1016/j.foodchem.2014.01.115

[43] Dai W, Ruan C, Zhang Y, Wang J, Han J, Shao Z, Sun Y, Liang J. Delivery of green tea catechin and epigallocatechin gallate in liposomes incorporated into low-fat hard cheese. J Funct Foods. 2020;65:103732. https://doi.org/10.1016/j.jff.2019.103732

[44] Fujiki H, Suganuma M. Green tea: An effective synergist with anticancer drugs for tertiary cancer prevention. Cancer Lett. 2012;324:119–125. https://doi.org/10.1016/j.canlet.2012.05.012

[45] Al-Sayed E, Abdel-Daim MM. Analgesic and anti-inflammatory activities of epicatechin gallate from *Bauhinia hookeri*. Drug Dev Res. 2018;79:157–164. https://doi.org/10.1002/ddr.21430

[46] Yu Y, Deng Y, Lu BM, Liu YX, Li J, Bao JK. Green tea catechins: A fresh flavor to anticancer therapy. Apoptosis. 2014;19(1):1-18. https://doi.org/10.1007/s10495-013-0908-5

[47] Baba S, Osakabe N, Natsume M, Muto Y, Takizawa T, Terao J. In vivo comparison of the bioavailability of (+)-catechin, (-)-epicatechin and their mixture in orally administered rats. J Nutr. 2001;131(11):2885-2891. https://doi.org/10.1093/jn/131.11.2885

[48] Song Q, Li D, Zhou Y, Yang J, Yang W, Zhou G, Wen J. Enhanced uptake and transport of (+)-catechin and (-)-epigallocatechin gallate in niosomal formulation by human intestinal Caco-2 cells. Int J Nanomedicine. 2014;9:2157-2165. https://doi.org/10.2147%2FIJN.S59331

[49] Cai ZY, Li XM, Liang JP, Xiang LP, Wang KR, Shi YL, Yang R, Shi M, Ye JH, Lu JL, Zheng XQ, Liang YR. Bioavailability of tea catechins and ıts ımprovement. Molecules. 2018;23(9):2346. https://doi.org/10.3390%2Fmolecules23092346

[50] Mazyed EA, Helal DA, Elkhoudary MM, Abd Elhameed AG, Yasser M. Formulation and optimization of nanospanlastics for ımproving the bioavailability of green tea epigallocatechin gallate. Pharmaceuticals (Basel). 2021;14(1):68. https://doi.org/10.3390/ph14010068

[51] Cardoso RV, Pereira PR, Freitas CS, Paschoalin VMF. Trends in drug delivery systems for natural bioactive molecules to treat health disorders: The ımportance of nano-liposomes. Pharmaceutics. 2022;14(12):2808. https://doi.org/10.3390/pharmaceutics14122808

[52] Kyriakoudi A, Spanidi E, Mourtzinos I, Gardikis K. Innovative delivery systems loaded with plant bioactive ıngredients: Formulation approaches and applications. Plants (Basel). 2021;10(6):1238. https://doi.org/10.3390/plants10061238.