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Characterization of Spanlastic System Loaded Green Tea Extract as Antioxidant for Skin

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Abstract

Background*: Green tea possesses abundant polyphenols that exert antioxidant activity. However, green tea's hydrophilicity and instability limit its penetration into the skin layers. Recently, a non-ionic surfactant-based elastic nanovesicular system called spanlastic can enhance the delivery of hydrophilic and unstable substances. Spanlastic composed of vesicle builder and edge activator, which influence the characteristics of the vesicle.* ***Objective****: The study aimed to evaluate the influence of the ratio of the components on the characterization of green tea extract-loaded spanlastic using three different weight ratio of vesicle builder and edge activator that is 7:3, 8:2, and 9:1.* ***Methods****: Spanlastic is prepared by ethanol injection methods using Span 60 as vesicle builder (VB) and Tween® 60 as edge activator (EA). The characterization includes visually observed organoleptic, particle size (PS) and polydispersity index (PDI) using dynamic light scattering, entrapment efficiency (EE) and drug loading (DL) using total phenolic content assay. The most optimum ratio will be tested its zeta potential value using Zetasizer and viscosity using Brookfield Cone and Plate.* ***Results****: Selected spanlastic formula composed of Span 60 and Tween® 60 at a weight ratio of 8:2 has given characteristics as follows: entrapment efficiency 60.85±1.70%; drug loading 11.07±0.65%; the particle size is 419.70±7.42 nm; and PDI value 0.26±0.05. The prepared spanlastic has a greenish liquid form, with a zeta potential value of 28.53±2.78 mV and viscosity of 14.65±0.32 cP.* ***Conclusion****: The optimum weight ratio of vesicle builder and edge activator for green tea extract spanlastic is Span 60:Tween® 60 8:2.*

Keywords*: spanlastic, green tea extract, vesicle-based delivery system, characterization, antioxidants*

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INTRODUCTION

Skin is the outermost part of the human body which mainly acts as a barrier against the external environment. It also protects the skin from microorganisms and prevents the water from evaporating from the skin (Martini, Nath and Bartholomew, 2018). As time passed, the natural process of skin aging occurred causing visible changes in the skin structure, such as loss of elasticity, fine lines, and dryness. The intrinsic factor such as cellular metabolism and external factors such as radiation of ultraviolet (UV) light can accumulate free radicals and induce matrix metalloproteinase production, which is known as the collagen degrading enzyme. When the amount of free radicals has exceeded the number of antioxidants, oxidative damage happened. Therefore, an antioxidant is essential to scavenge free radicals.

Antioxidants naturally present on plants, as secondary plant metabolites called polyphenols. The tea plant (Camellia sinensis L.) contains abundant polyphenols compound and shows potential as anti-aging. Polyphenols are especially present the most in green tea. Green tea polyphenols are dominated by catechin compounds: epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC). The most abundant catechin compounds are EGCG, therefor its physicochemical characteristics is further used to represent green tea extract in this study . The physicochemical characteristics of EGCG are limiting the penetration to the skin, as it is very hydrophilic and unstable toward the light. Therefore green tea extract needs a suitable delivery system, to increase its penetration into the skin.

A non-ionic surfactant vesicular delivery system called spanlastic has been emerging as the novel delivery system suitable for delivering hydrophilic substances. The elasticity of the system has been shown to improve the entrapment efficiency of the active substances when compared with the conventional niosomes (Kakkar and Kaur, 2011a). The flexible membrane enables it to penetrate through small-sized pores of the skin, increasing active ingredients penetration. Besides that, the vesicle also act as penetration enhancer, increase penetration through fusion or adsorption with the stratum corneum, and through the hair follicle. The addition of an edge activator also increases skin diffusion by increasing the vesicle capacity to bind water, preventing water evaporation, and hydrating the skin enhancing its suitability to be applied on the skin for topical uses (Alaaeldin *et al.*, 2021; Rathod *et al.*, 2021).

Spanlastic is composed of a non-ionic surfactant as the vesicle builder and an edge activator that gives elasticity to the vesicle membrane. The formation of spanlastic is depends on three determining factors that is hydrophilic-lipophilic balance (HLB), critical packing parameter (CPP), and phase transition temperature (Tc). Span 60 is chosen as the non-ionic surfactant that fulfills all the requirements to form the vesicle. It has a low HLB value of 4.7 with a long alkyl chain. The CPP value also goes between 0.5-1.0 so it can form vesicles spontaneously. The Tc value of Span 60 is also pretty high at 53°C implying that the orderly stated bilayer molecules are present in the membrane (Ag Seleci *et al.*, 2016; Khoee and Yaghoobian, 2017; Mazyed *et al.*, 2021). Tween® 60 is chosen as the edge activator because of its hydrophilicity with an HLB value of 14.9 causing destabilization of the vesicles. The previous research also showed that a combination of Span 60 and Tween® 60 produces spanlastic with the highest entrapment of active ingredients (Alaaeldin *et al.*, 2021; Mazyed *et al.*, 2021).

Hence, the objective of this study was to prepare green tea extract-loaded spanlastic using various ratios of vesicle builder and edge activator to see how it influences the characterization of spanlastic. The characterization of spanlastic comprises entrapment efficiency, drug loading, particle size, polydispersity index, and zeta potential (Kakkar and Kaur, 2011a).

MATERIALS AND METHODS

Materials

Green tea leaf (Tea Heaven, Indonesia), Span 60 (Croda, UK), Tween® 60 (Croda, UK), Absolute Alcohol (Merck, Germany), Deionized water, Folin-Ciocalteu's phenol reagent (Merck, Germany), Sodium Carbonate (Merck, Germany), Gallic acid anhydrous (Merck, Germany).

Method

Preparation of green tea ethanol extract

Green tea leaf was processed using a grinder/blender to obtain a finely powdered green tea leaf. About 12 grams of powdered green tea leaf is weighed down and added with 720 ml 75% ethanol (1:60 w/v). The mixture was then heated in a thermostated water bath at 90°C for 10 minutes. After 10 minutes, the resultant infusion is filtered using the Buchner funnel vacuum filtration method with Whatmann filter paper 40. The filtrate was concentrated by a rotary evaporator under reduced pressure until the thick extract is obtained. Then, the extract continued to

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be dried using a freeze dryer. The resultant powdered green tea ethanol extract is stored at room temperature in a dark bottle to prevent any light exposure (Hu, Zhou and Chen, 2009).

Preparation of green tea extract spanlastic

The ethanol injection method was employed to fabricate the spanlastic system. The method has been successfully developed in a spanlastic system in previous research. Accurately weight Tween® 60, as stated in Table 1, was added into deionized water and heated at 60˚C. The organic phase consisting of Span 60 and powdered green tea extract dissolved in absolute ethanol was also prepared. The organic phase was injected dropwise into the water phase on continuous stirring until the milky dispersion is formed. The heating was continued for 30 minutes to evaporate the excess ethanol from the dispersion completely. The formed spanlastic was left overnight at 4˚C for complete maturation until used in further studies (Fahmy *et al.*, 2018, 2019; Guimarães *et al.*, 2020; Mazyed *et al.*, 2021).

Characterization of green tea ethanol extract spanlastic

Organoleptic

The physical appearance of the green tea extract spanlastic was visually observed regarding its consistency, color, odor, and consistency soon after being kept refrigerated overnight.

Particle size and polydispersity index (PDI)

Green tea ethanol extract spanlastic was diluted with deionized water (1:100) and homogenized at 25˚C, and then the particle size was determined using Malvern Zetasizer Nano.

Entrapment efficiency & drug loading

Entrapment efficiency was determined by analyzing the total phenolic compound on the spanlastic. About 1 ml of green tea ethanol extract spanlastic is centrifugated at 13,000 rpm for 30 minutes at 4˚C to separate the free phenolic compound (Badria *et al.*, 2020). Then, the free phenolic compound on the supernatant was analyzed with the Folin-Ciocalteu method.

The standard curve of gallic acid was prepared to assess the total phenolic compound through a different concentration (20-100 ppm) of gallic acid standard solution in water. A saturated sodium carbonate solution (75 g/L) and 0.2 mol/L Folin-Ciocalteu's reagent was prepared. About 20 mL of 2 mol/L Folin-Ciocalteu's reagent was diluted with deionized water until the volume reaches 200 mL.

Precisely pipetted 0.5 ml of the green tea ethanol extract spanlastic supernatant sample and a standard solution are transferred to the amber vial and wrapped in aluminium foil, then added with 2.5 mL 0.2 mol/L Folin Ciocalteu's reagent. The mixture is left at room temperature for 4 minutes in the dark conditions. Then, about 2 mL of saturated sodium carbonate solution (75 g/L) was added to the mixture and left for 2 hours in the dark at room temperature. Deionized water was used as a blank solution. The absorbance was measured after 2 hours using UV-spectrophotometer at 764 nm against the blank solution. Then, total phenolic content was reported as gallic acid equivalent (GAE/gram) (Zhao *et al.*, 2019).

The total drug content, which consisted of the unentrapped and entrapped drug, was also determined to calculate the entrapment efficiency. About 1 mL of green tea ethanol extract spanlastic was added to 100 mL isopropyl alcohol. The mixture was homogenized and then processed to estimate the total phenolic content using the Folin-Ciocalteu method previously described (Mazyed *et al.*, 2021).

% EE was calculated based on equation %EE = (TD GTE-TF GTE)/TD GTE x 100

Drug loading was calculated using equation %DL = (TD GTE-TF GTE)/TS x 100 where TD was the total drug of green tea extract, TF was the total free green tea extract, and TS was the total surfactant used in the formula (Sallam *et al.*, 2021).

Table 1. Green tea extract-loaded spanlastic formula

Material	Function	Weight (w/w)		
		SPL 1 (9:1)	**SPL 2 (8:2)**	**SPL 3 (7:3)**
Green tea extract	Active ingredient	50 mg	50 mg	50 mg
Span 60	Vesicle builder	180 mg	160 mg	140 mg
Tween® 60	Edge activator	20 mg	40 mg	60 mg

Note:
SPL 1 = formula of green tea extract spanlastic with the weight ratio of 9:1
SPL 2 = formula of green tea extract spanlastic with the weight ratio of 8:2
SPL 3 = formula of green tea extract spanlastic with the weight ratio of 7:3
The total amount of surfactants used was 200 mg
Total volume of spanlastic was 25 ml

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Zeta potential

The most optimal formula of green tea ethanol extract spanlastic was diluted with deionized water (1:100) and homogenized at 25˚C, and the zeta potential was determined using Malvern Zetasizer Nano.

Viscosity

The viscosity of the green tea extract spanlastic was measured using the Brookfield Cone and Plate using spindle 41. Approximately 0.5-2.0 ml sample was put on the sample cup, then measured at 25˚C.

Antioxidant activity by DPPH Radical Scavenging Method

The sample was separated first using a centrifuge at 13,000 rpm for 30 minutes. The resulting supernatant was used to make a series of concentrations to react with 0.004% DPPH ethanolic solution. About 2 ml of 0.004% DPPH ethanolic solution was added to the 2 ml sample. Then the mixture was left under dark conditions for 30 minutes. The absorbance measurement was performed at 517 nm using Spectrophotometer UV-Vis. The inhibition was calculated using the equation as follows % inhibition = (Ac-As)/Ac x100% where Ac was the absorbance of the control and As was the absorbance of the sample.

Data analysis

All measurements were conducted in triplicate, and data were expressed as mean ± SD. The data was analyzed using a One-way analysis of variance (ANOVA), followed by the Tukey test. A value of $P < 0.05$ was considered significantly different. The IBM SPSS Statistics 25 software was used for data analysis.

RESULTS AND DISCUSSION

Preparation of green tea extract spanlastic

The green tea extract-loaded spanlastic was successfully prepared using the ethanol injection method with Span 60 as the vesicle builder and Tween® 60 as the edge activator. Three main factors influenced the formation of spanlastic. The surfactant's hydrophilic-lipophilic balance (HLB) value and the critical packing parameter (CPP) needed to be considered. A surfactant with an HLB value between 4-8 and a CPP value between 0.5-1.0 reflected the ability of the surfactant to assemble vesicles by itself in the absence of cholesterol. Lastly, the phase transition temperature (Tc) was correlated with the permeability of the vesicle membrane. The higher the Tc value was, the more vesicle was stable and not porous.

The ethanol injection method was suitable for forming large unilamellar vesicles (LUV) of spanlastic, to be able to entrap more hydrophilic substances in its core (Durak *et al.*, 2020). Moreover, the addition of ethanol decreased the vesicle thickness, leading to an increase in drug partition and a smaller size of vesicles (Alnusaire *et al.*, 2021; Mahmoud A Elgewelly *et al.*, 2022).

Characterization of green tea ethanol extract spanlastic

Organoleptic

After being stored overnight, the green tea extract-loaded spanlastic was observed visually regarding color, odor, and consistency. The visually observed green tea extract-loaded spanlastic shown in Figure 1 showed no differences between its color, odor, or consistency even when formulated with different ratios of Span 60 (vesicle builder) and Tween® 60 (edge activator). All formula of green tea extract-loaded spanlastic depicted green-colored odorless liquid, as detailed in Table 2.

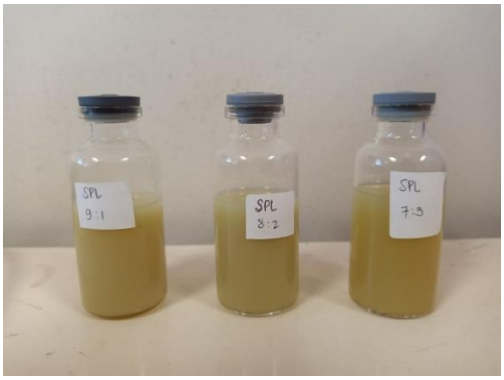

Figure 1. Green tea extract-loaded spanlastic with different ratios of vesicle builder and edge activator: SPL 1 (9:1); SPL 2 (8:2); and SPL 3 (7:3) from left to the right side

Table 2. Spanlastic formula organoleptic

Formula	Organoleptic Parameter		
	Color	**Odor**	**Consistency**
SPL 1 (Span 60: Tween® 60 9:1)	Green	Odorless	Liquid
SPL 2 (Span 60: Tween® 60 8:2)	Green	Odorless	Liquid
SPL 3 (Span 60: Tween® 60 7:3)	Green	Odorless	Liquid

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Table 3. Result of particle size and polydispersity index measurement

Formula	Particle size ±SD (nm)*	PDI ±SD*
SPL 1 (Span 60: Tween® 60 9:1)	1283.05 ± 15.10	0.50 ± 0.04
SPL 2 (Span 60: Tween® 60 8:2)	419.70 ± 7.42	0.260 ± 0.05
SPL 3 (Span 60: Tween® 60 7:3)	244.20 ± 15.34	0.30 ± 0.01

*Particle size and PDI data were result from triplicate measurement

Table 4. Entrapment efficiency and drug loading of the green tea extract-loaded spanlastic

Formula	EE±SD (%)*	DL ±SD (%)*
SPL 1 (Span 60: Tween® 60 9:1)	61.46 ± 0.11	12.04 ± 0.09
SPL 2 (Span 60: Tween® 60 8:2)	60.85 ± 1.70	11.07 ± 0.65
SPL 3 (Span 60: Tween® 60 7:3)	39.95 ± 1.11	5.31 ± 0.28

*%EE and %DL data were result from triplicate measurement

Particle size and polydispersity index (PDI)

Designing a vesicular system within the nanometer range was essential to ensure the penetration of the system through the deeper skin layer. Several factors can affect the size of the vesicular system. Developing a small particle size will produce a larger surface area available for the diffusion process (Enas Elmowafy *et al.*, 2019; Alaaeldin *et al.*, 2021). Non-ionic surfactants, as the vesicle builder, can achieve a better entrapment of the active substances when incorporated in large amounts. But it also increased the diameter of the vesicle, resulting in a bigger vesicle size. A particle size below 700 nm has been reported to be able to penetrate the deeper skin layer and exert a beneficial effect on UVB treatment, psoriasis treatment, and anti-inflammatory effect (Farghaly *et al.*, 2017; Enas Elmowafy *et al.*, 2019; Elhabak, Ibrahim and Abouelatta, 2021)

From Table 3, increasing the Span 60 amount has significantly enlarged the diameter of the vesicle. While the concentration of Span 60 increased, the concentration of Tween® 60 decreased. This low concentration of edge activators was inadequate to cover the whole surface area, leading to the agglomeration of some vesicles to reduce their surface area, so the Tween® 60 will be sufficient to protect it. This agglomeration tendency will lead to the formation of a larger vesicle size. On the contrary, the increasing amount of edge activator, Tween® 60, has decreased particle size. This has been correlated to lower the surface tension between the two phases, leading to particle partition to a smaller vesicle. Another research also stated the possibility of mixed micelles formation in the presence of a high-concentration edge activator. It was also necessary to note that the preparation of spanlastic using ethanol has also affected the particle size (Shaaban *et al.*, 2019; Shamma *et al.*, 2019a; Badria and Mazyed, 2020). The addition of ethanol has decreased the vesicle membrane thickness, modifying the net charge of the vesicle and providing steric stabilization, leading to a smaller vesicle size (Kakkar and Kaur, 2011b; Alaaeldin *et al.*, 2021).

The particle size distribution was reflected by the polydispersity index (PDI) value. The formulas showed PDI values ranging from 0.30-0.50, indicating a homogenous system with a low tendency toward aggregation (Abbas and Kamel, 2020; Elhabak, Ibrahim and Abouelatta, 2021).

Entrapment efficiency & drug loading

Entrapment efficiency is the essential factor that ensures the drug is successfully entrapped by the vesicle, to optimally deliver the drug. The non-ionic surfactant and edge activators, as the vesicular structure builder, is the essential determining factor of the system entrapment efficiency. Their amount together has shown significant effects on the entrapment efficiency of the system.

Based on Table 4, it can be observed that by increasing the amount of vesicle builder, Span has significantly increased the entrapment efficiency along with the drug loading. The only insignificant difference is the entrapment efficiency between SPL 1 and SPL 2, despite both having significantly different vesicle sizes. On the contrary, the negative effect is observed after increasing the amount of edge activator. The hydrophilic characteristic of edge activators leads to pore formation in the bilayer membrane, thus reducing its entrapment (Shamma *et al.*, 2019b; Elhabak, Ibrahim and Abouelatta, 2021).

The combination of the lipophilic and hydrophilic surfactant has developed a mixed HLB value. According to the literature, the best HLB value to prepare spanlastic is in the range of 4-8 (Ag Seleci *et al.*, 2016). It is essential to ensure that the concentration of edge activators should be at a certain point, since excess edge activators cause the formation of micelles and/or mixed micelles, instead of vesicle formation. The micellar structure will lead to drug leakage, resulting in

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lower entrapment (Abbas and Kamel, 2020; Mahmoud A. Elgewelly *et al.*, 2022). While entrapment efficiency is not affected by the number of active substances added to the system due to the maximum capacity of the non-ionic surfactant to entrap the substances in a fixed amount (Elhabak, Ibrahim and Abouelatta, 2021).

Zeta potential

Based on the measurement result of particle size, PDI, %EE, and %DL it was concluded that SPL 2 has given the most suitable characteristic for the delivery of green tea extract. The measurement of zeta potential was undertaken on SPL 2 by using Malvern Zetasizer. Zeta potential value itself can reflect the stability of the system by measuring the net charge of the vesicles. The result obtained from the measurement is -28.53 ± 2.78 mV, as seen in Table 5. Despite the formula does not contain any charged molecules, the negative zeta potential was obtained as the result of dispersion medium hydroxyl ions adsorption on the vesicle surface. The charged vesicle is considered to have a low tendency towards aggregation and fusion because it will cause repulsion between vesicles. The system with a zeta potential value of around ± 30 mV is considered to be stable (E Elmowafy *et al.*, 2019; Badria and Mazyed, 2020; Elhabak, Ibrahim and Abouelatta, 2021).

Table 5. Zeta potential result of SPL 2

Formula	Zeta potential±SD (mV)
SPL 2 (Span 60: Tween® 60 8:2)	-28.53 ± 2.78

*data were result from triplicate measurement

Viscosity

Viscosity measurement is an essential parameter that reflects the system's suitability as the form of topical dosage. The result of viscosity measurement towards SPL 2 showed a low viscosity of 14.65 ± 0.32 cPs, as seen in Table 6. The watery texture of spanlastic is not suitable for the topical delivery dosage form, as it has a low residence time on the skin. Several previous research has stated that spanlastic incorporation into gel dosage form is increasing its adherence and spreadability on the skin, leading to better skin penetration (Goyal *et al.*, 2015; Enas Elmowafy *et al.*, 2019; Mahmoud A. Elgewelly *et al.*, 2022).

Table 6. Viscosity of SPL 2

Formula	Viscosity±SD (cPs)
SPL 2 (Span 60: Tween® 60 8:2)	14.65 ± 0.32

*data were result from triplicate measurement

Antioxidant activity by DPPH Method

The antioxidant activity is evaluated through the inhibition concentration of 50% DPPH radical (IC_{50}) value. The IC_{50} of green tea extract spanlastic and gallic acid as control shows a very strong antioxidant activity (IC_{50}<50 ppm). The strong antioxidant activity related to the gallate group that present on position 3 EGCG catechin structure and hydroxyl group on 5' EGC structure (Guo *et al.*, 1999; Budiman *et al.*, 2019).

Table 7. IC_{50} value by DPPH Radical Scavenging Method

Formula	IC_{50}±SD (ppm)
Gallic acid (control)	3.34 ± 0.03
SPL 2	7.63 ± 0.07

*data are result from triplicate measurement
*data were result from triplicate measurement

CONCLUSION

In the present study, the green tea extract is successfully loaded in the vesicle-based delivery system spanlastic. The ratio of vesicle builder and edge activator does have an important role by significantly affecting the characterization of spanlastic. SPL 2 formula with an Span 60:Tween® 60 80:20 ratio showed the most optimal characteristic in particle size, PDI, entrapment efficiency, and drug loading for topical dosage forms. Moreover, through DPPH Radical Scavenging assay it has proven to possess a potent antioxidant activity with IC_{50} below 50 ppm that ensuring its effect as antiaging. However, spanlastic has a low viscosity, incorporation into another vehicle such as gel is encouraged to enhance its penetration into the skin. The described green tea extract-loaded spanlastic unravels its potential in future research to be used as the anti-aging topical dosage form.

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REFERENCES

Abbas H, Kamel R. Potential role of resveratrol-loaded elastic sorbitan monostearate nanovesicles for the prevention of UV-induced skin damage. J Liposome Res 2020;30:45–53. https://doi.org/10.1080/08982104.2019.1580721

Ag Seleci D, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticular drug carriers: Fundamentals and recent applications. J Nanomater 2016;2016. https://doi.org/10.1155/2016/7372306.

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;16:133–45. https://doi.org/10.2147/IJN.S289828.

Alnusaire TS, Sayed AM, Elmaidomy AH, Al-Sanea MM, Albogami S, Albqmi M, et al. An in vitro and in silico study of the enhanced antiproliferative and pro-oxidant potential of olea europaea l. Cv. arbosana leaf extract via elastic nanovesicles (spanlastics). Antioxidants 2021;10:1–18. https://doi.org/10.3390/antiox10121860.

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 Devel Ther 2020;14:3697–721. https://doi.org/10.2147/DDDT.S265167.

Badria FA, Fayed HA, Ibraheem AK, State AF, Mazyed EA. Formulation of sodium valproate nanospanlastics as a promising approach for drug repurposing in the treatment of androgenic alopecia. Pharmaceutics 2020;12:1–27. https://doi.org/10.3390/pharmaceutics12090866.

Durak S, Rad ME, Yetisgin AA, Sutova HE, ... Niosomal drug delivery systems for ocular disease—recent advances and future prospects. Nanomaterials 2020.

Elgewelly MA, Elmasry SM, Sayed NS El, Abbas H. Resveratrol-Loaded Vesicular Elastic Nanocarriers Gel in Imiquimod-Induced Psoriasis Treatment: In Vitro and In Vivo Evaluation. J Pharm Sci 2022;111:417–31. https://doi.org/https://doi.org/10.1016/j.xphs.2021.08.023.

Elhabak M, Ibrahim S, Abouelatta SM. Topical delivery of l-ascorbic acid spanlastics for stability enhancement and treatment of UVB induced damaged skin. Drug Deliv 2021;28:445–53. https://doi.org/10.1080/10717544.2021.1886377

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.

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. https://doi.org/10.1208/s12249-019-1306-2.

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

Farghaly DA, Aboelwafa AA, Hamza MY, ... Topical delivery of fenoprofen calcium via elastic nano-vesicular spanlastics: Optimization using experimental design and in vivo evaluation. AAPS PharmSciTech 2017. https://doi.org/10.1208/s12249-017-0771-8.

Goyal G, Garg T, Malik B, Chauhan G, Rath G, Goyal AK. Development and characterization of niosomal gel for topical delivery of benzoyl peroxide. Drug Deliv 2015;22:1027–42. https://doi.org/10.3109/10717544.2013.855277.

Guimarães D, Noro J, Loureiro A, Lager F, Renault G, Cavaco-Paulo A, et al. Increased encapsulation efficiency of methotrexate in liposomes for rheumatoid arthritis therapy. Biomedicines 2020;8:1–15. https://doi.org/10.3390/biomedicines8120630.

Hu J, Zhou D, Chen Y. Preparation and antioxidant activity of green tea extract enriched. J Agric Food Chem 2009;57:1349–53.

Kakkar S, Kaur IP. Spanlastics-A novel nanovesicular carrier system for ocular delivery. Int J Pharm 2011a;413:202–10. https://doi.org/10.1016/j.ijpharm.2011.04.027.

Khoee S, Yaghoobian M. Niosomes: a novel approach in modern drug delivery systems. Elsevier Inc.; 2017. https://doi.org/10.1016/b978-0-323-46143-6.00006-3.

Martini FH, Nath JL, Bartholomew EF. Fundamentals of Anatomy & Physiology. 11th ed. Pearson; 2018.

Mazyed EA, Helal DA, Elkhoudary MM, ... Formulation and Optimization of nanospanlastics for improving the bioavailability of green tea epigallocatechin gallate. Pharmaceuticals 2021.

Rathod S, Arya S, Shukla R, Ray D, Aswal VK, Bahadur P, et al. Investigations on the role of edge activator upon structural transitions in Span vesicles. Colloids Surfaces A Physicochem Eng Asp 2021;627:127246. https://doi.org/10.1016/j.colsurfa.2021.127246.

Sallam NM, Sanad RAB, Ahmed MM, Khafagy ES, Ghorab M, Gad S. Impact of the mucoadhesive lyophilized wafer loaded with novel carvedilol

nano-spanlastics on biochemical markers in the heart of spontaneously hypertensive rat models. Drug Deliv Transl Res 2021;11:1009–36. https://doi.org/10.1007/s13346-020-00814-4.

Shaaban M, Nasr M, Tawfik AA, Fadel M, ... Novel bergamot oil nanospanlastics combined with PUVB therapy as a clinically translatable approach for vitiligo treatment. Drug Deliv … 2019. https://doi.org/10.1007/s13346-019-00653-y.

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 2019a;29:283–90. https://doi.org/10.1080/08982104.2018.1552706

Zhao C, Tang G, Cao S, Xu X, Gan R, Liu Q. Phenolic Profiles and Antioxidant Activities of 30 Tea Infusions from Green , Black , Oolong , White , Yellow and Dark Teas. Antioxidants 2019:215

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