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Impact of Formulation Variables on Meloxicam Spanlastics Preparation

Mohammed Khalil[1] and Lubna Abdalkarim Sabri [*,2]

[1]Ministry of Health, Babylon Health Directorate, Babylon, Iraq.
[2] Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Iraq.

[*]**Corresponding author**
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Abstract

Spanlastic is a modern drug delivery that combines vesicular and nanoparticulate characteristics with numerous advantages over topical applied conventional vesicular systems in terms of stability, penetration flexibility, and targeting. Meloxicam (MX) is a potent non steroid anti-inflammatory drug that is frequently utilized for the short- and long-term treatment of chronic pain and inflammatory diseases including rheumatoid arthritis. However, the oral administration of MX often includes several adverse effects, including gastrointestinal disturbances and ulceration. Thus, the aim is a preparation of proper formula for MX-loaded spanlastics via studying the formulation variables that may affect their properties using the ethanol injection method. Variables include; the type and volume of organic phase solvent (ethanol, chloroform), the type of edge activators (tween 80, brij 35, cremophor RH40), span®60: edge activator ratio, the amount of MX were studied for their impact on particle size, polydispersity index, and entrapment efficiency. The formula that was selected showed sustained release for six hours, entrapment efficiency of 70.66±1.15%, zeta potential (-4.51 mV), and particles that were 495±9.9 nm in size. Overall, the results indicated that spanlastics had the potential carrier for medicine delivery systems.

Keywords: Edge activators, Injection method, Meloxicam, Spanlastic, Span 60.

Introduction

Novel drug delivery system called spanlastic which combines vesicular and nanoparticulate characteristics [(1)]. The name "Spanlastic" is derived from "span add to elastic," in which the hydrophobic or hydrophilic medication can be contained in the outer lipid layer or inner hydrophilic core, respectively [(2)]. The nonionic surfactant, span, and edge activator (EA) are vital components of spanlastic, which promote vesicle entrapment effectiveness and establishment through steric stability. Furthermore, they enhance drug bioavailability through their ability to increase drug penetration across biological membranes accompany by a sustained or controlled manner of drug release at a target site [(3)]. The EA is single chain surfactant which are hydrophilic wetting agent, like tweens, polyvinyl alcohol, and Brij which can reduce interfacial tension to stabilize vesicular bilayer, thus promote spanlastics elasticity and flexibilty leading to easy of vesicles deformation which can help penetration through skin layers [(1)].

They are structurally similar to traditional liposomes but are more chemically stable. Spanlastics or modified niosome, are biodegradable, nonimmunogenic, flexible, and deformable walled nano-vesicular systems that differ from ordinary niosomes in that they only contain nonionic surfactants. They resemble transfersomes, which are very elastic and flexible liposomes [(4)].

Several studies on spanlastics have been successful in enhancing therapeutic efficiency and patient compliance [(1)]. Spanlastics are intended for enhanced bioavailability and targeted different administration routes like the ocular [(5)], oral [(3)], nasal [(6)], and transungual [(7)]. Transdermal delivery of combined letrozole and quercetin-loaded spanlastics revealed enhancing their breast cytotoxic effects by reducing the harmful adverse effects by reasonable flux and permeation with sustained drugs release for 24 h through the rat skin [(8)].

Meloxicam (MX) is a very potent non-steroidal anti-inflammatory medication (NSAID) from the oxicamm derivatives enolic acid class. Meloxicam is used as an anti-inflammatory, analgesic, and antipyretic agent, it is also emerging as a promising drug for the treatment of Alzheimer's disease and cancer [(9,10)]. The molecular weight of MX is 351.4 g/mol, and its dissociation

constants (pKa) are 1.1 and 4.2. Its Log P (P; Octanol/ Water partition coefficient) is 3.43 and its water solubility is 0.012 mg/ml which means it is practically insoluble in water [11].

However, oral administration of MX often includes several adverse effects, such as gastrointestinal disturbances and ulceration. Thus, transdermal drug delivery systems are preferred [12]. To ensure maximum medication action, it must get through the skin's permeability barrier and extend the drug's time in the skin's layers to have enough time to overcome the skin absorption rate-limiting step [13]. Thus, one of the approaches to achieve this is encapsulating MX in elastic surfactants-based vesicular nanocarriers (spanlastics).

The aim of this research was to study impact of different formulation factors to optimize meloxicam-loaded spanlastics.

Materials and Methods

Materials

Meloxicam MX powder (Baoji Guokang Bio-Technology Co., Ltd), Cremophor® RH40 (Basf, Germany), Span® 60 (Xi'an Sonwu Biotech Co.Ltd, China), Brij®35 (Shanghai Macklin Biochemical Co., Ltd, China), Tween® 80 (Thomas baker, Mumbai, India), Methanol (Thomas Baker, India), Ethanol **(**Sasma, Netherlands), Chloroform (Thomas baker, Mumbai, India), Phosphate buffer pH 7.4 (PBS)(Himedia, India), Dialysis membrane M.wt 8000-14000(Special products laboratory, USA).

Methods

Preparation of MX- loaded spanlastics

The main steps of the injection method for spanlastic preparation were summarized in Figure 1. Briefly, MX and the appropriate quantity of Span®60 were dissolved in the organic phase, while the various formulations of Tween®80 or Brij®35, or Cremophore® RH40 as EA were dissolved in 15 mL of deionized water at a temperature of 65°C. A homogenizer was used to mix the aqueous solution at a speed of 2000 rpm for 15 minutes while the organic solution was added dropwise at a rate of 1 mL/ min. The completed mixture was held on the magnetic stirrer at room temperature for an additional one and quarter hour at a speed of 1000 rpm. The formulations were then stored in a refrigerator until further evaluations were done on them [14]. Twelve formulas were prepared to study the effect of formulation variables as illustrated in Table 1.

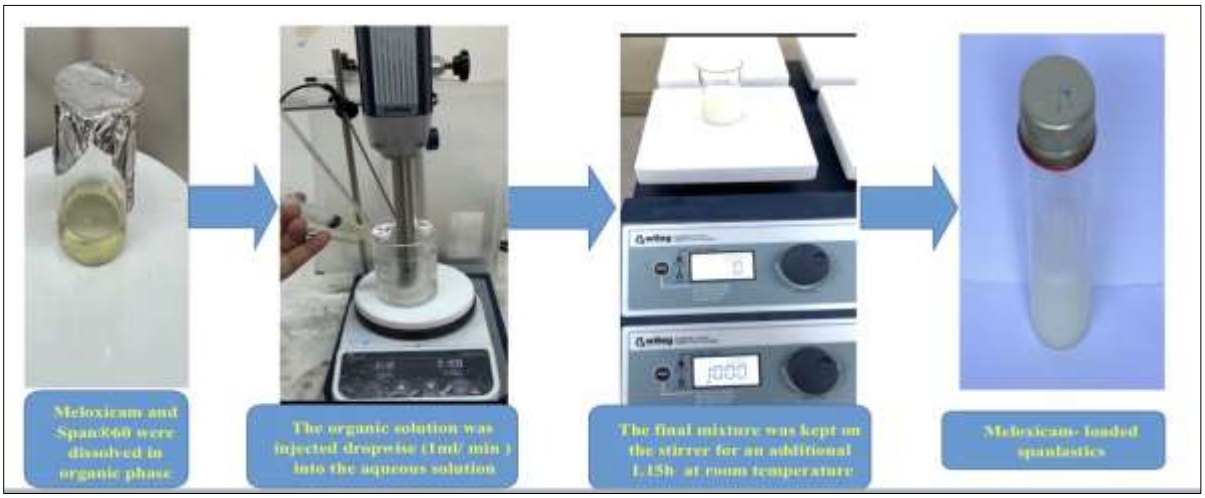

Figure 1. The main procedures involved in creating MX-loaded spanlastics.

Table 1. Composition of Meloxicam-loaded Spanlastics to Study Variable Formulation Factors

Formula code	Drug (mg)	Span® 60(mg)	Tween® 80 (mg)	Cremophore® RH40(mg)	Brij ®35 (mg)	Chloroform: ethanol (mL)	The volume of the internal phase (ml)	The volume of the external phase (mL)
SF1	10	350	39	__	__	0:6	6	15
SF2	10	350	39	—	—	4:2	6	15
SF3	10	350	39	—	—	2:4	6	15
SF4	10	350	39	—	—	3:3	6	15
SF5	10	350	39	—	—	4:2	12	15
SF6	10	350	39	—	__	4:2	9	15
SF7	10	350	—	39	—	4:2	6	15

SF8	10	350	__	__	39	4:2	6	15
SF9	10	350	87.5	__	__	4:2	6	15
SF10	10	350	150	__	__	4:2	6	15
SF11	15	350	39	__	__	4.2	6	15
SF12	5	350	39	__	__	4.2	6	15

Evaluation of MX-loaded spanlastics formulations

Determination of vesicle size and polydispersity index (PDI)

The size of the vesicles or particles used in transdermal administration dosage forms is crucial to their ability to enter the skin; smaller vesicles or particles do so more deeply and so improve transdermal delivery. Based on the light scattering fluctuations principle of Zetasizer Nano, One ml of each formulation was tested for vesicle size and PDI. The near zero or lower PDI value (less than 0.5) means a monodisperse droplet, meanwhile a higher PDI value closer to 1 means a wide range of droplet size [(15)].

Determination of MX entrapment efficiency

Utilizing the indirect method and ultracentrifugation, the entrapment efficiency (EE%) of MX-loaded spanlastics was calculated. MX-loaded spanlastic dispersion (1.5 mL) was put in a cooling centrifuge at 4 °C and 15,000 rpm for 1.15 hours. Utilizing a UV-Visible absorbance spectrophotometer to read at the maximum absorbance wavelength of MX in PBS and after appropriate dilutions, spectrophotometric analysis was utilized to calculate the supernatant's content of free MX. To calculate the (EE%) of MX-loaded spanlastics, the equation was utilized [(16)].

% EE = [(Total amount of drug − free drug in supernatant)/ Total amount] × 100 .. (Eq. 1)

Release of MX-loaded spanlastics in-vitro study

Selected spanlastics formulations had in vitro drug release done to them. The amount of medication released after six hours was calculated using the dialysis bag method. Briefly, from the chosen spanlastic formulations, a predetermined spanlastic dispersion volume that was equivalent to two milligrams of meloxicam's was obtained and placed into dialysis bags. The dialysis bags were then put in a paddle-style (type II- dissolution apparatus) which contained 200 mL of fresh prepared PBS solution as the releasing medium to create a sink condition depending on our performed MX saturated solubilty study in PBS which was found to be 0.421±0.83 mg/mL. The paddles rotated at a rate of 100 revolutions per minute, and the temperature was kept at 37 ±0.2 °C. At time intervals (1, 2, 3, 4, 5, and 6 hours), 3 mL was taken out and replaced with a new PBS solution.

By measuring the absorbance of MX at 362 nm, its λ_{max}, in PBS and depending on the calibration curve equation (y = 0.051x - 0.0054) of MX that had previously been constructed in PBS by measuring the absorbance of different known MX concentration and then plot them versus each other. The plot showed straight line with high correlation coefficient (R^2=0.9995). The concentration and percent of MX released were measured in the withdrawal samples using spectrophotometry. The release experiments were carried out in triplicate [(17)].

Kinetic models

The in-vitro release data from selected spanlastic formulas were fitted to various kinetic equations using the DDsolver and Microsoft Excel® 2016 programs to determine the best-fit mechanism and kinetics order of meloxicam release from spanlastic formulations [(18)]**.** In this method, four kinetic models, i.e. Zero order, first-order, Higuchi, and Korsmeyer-Peppas kinetics.

Optimization of MX-loaded spanlastics

Selected formulas of spanlastics with the higher EE%, proper droplet size, and PDI. The optimum formula that showed sustained release characteristic were used for additional studies.

Zeta potential determination

The net charges of the selected MX-loaded spanlastic nano vesicular formulations obtained were calculated using their zeta potentials, which may be used to judge the stability of the vesicular formulations**.**

FTIR spectrum for the best meloxicam-loaded spanlastics formula

Testing the FTIR spectrum for the pure drug (meloxicam), Tween® 80, span® 60, and the physical mixture of these substances was done to test the compatibility between the materials used in the preparation of MX-loaded spanlastics. Additionally, the liquid form of the selected meloxicam-loaded spanlastics dispersion was examined for its FTIR spectrum. Tested samples were placed directly without any previous preparation onto the crystal area of Fourier transform infrared (FTIR) spectroscopy ((Shimadzu, Japan) that combined with the attenuated total reflectance (ATR) technique. Then, pressure arm was positioned above the sample and scanned over the range between 4000 - 400 cm^{-1} wavenumber at resolution of 8 cm [(19)].

Optical microscope morphology

One mL of the optimum formula dispersion in distilled water was examined under a light microscope at 100X magnifications to confirm the production of vesicles.

Statistical analysis

The analysis of variance (ANOVA) test was used to analyze the experiment results by using SPSS® version 26.0.0.0 software. A p-value of 0.05 or less ($p \leq 0.05$) was regarded as significant, and

0.05 or more (p>0.05) was regarded as non-significant. and the mean of the triplicate sample readings (±standard deviation) was used to represent the results.

Results and Discussion

Preparation of MX- loaded spanlastics

The entrapment efficiency, acceptable stable appearance, and uniform nanosized spanlastics were largely affected by the chemistry of the selected nonionic surfactant and other spanlastic additives. So, span®60 was selected as membrane forming nonionic surfactant own to its lipophilic long saturated alkyl chain, $C_{24}H_{46}O_6$, (its HLB value = 4.7) that can create stable single and/or multilamellar nanovesicles layers with good drug loading and stability compared to the other span types. Additionally, span®60 boosts interfacial tension reduction by edge activators resulting in nanosized spanlastic vesicles [1, 5, 6]. Twelve prepared formulas showed the appearance of a homogenous milky white liquid dispersion. The effect of different variables on the characteristics of vesicular spanlastics was investigated. It was found that vesicles size ranged from 1330±36.66 to 240 ±7.76 nm (Figure 2), and the PDI varied between 1.3±0.13 and 0.34 ±0.04 % (Figure 3), the PDI value greater than 0.5 indicate heterogeneous dispersion with broad wide vesicular size distribution. On the other hand, data for the % EE were between 70.66±1.15 and 31.33±1.52 % (Figure 4).

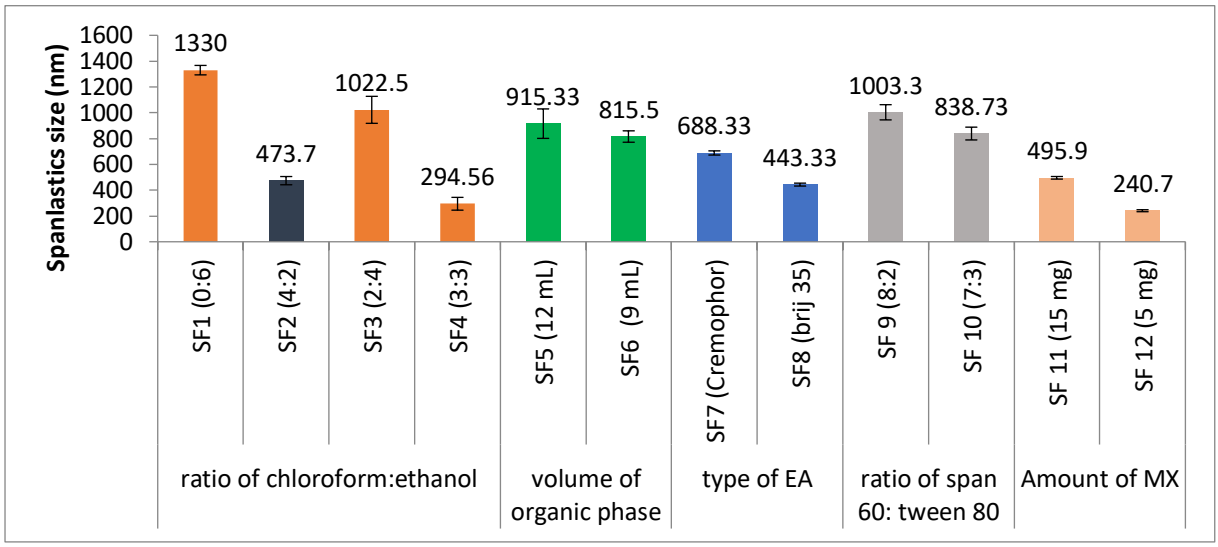

Figure2. The impact of formulation variables on the vesicular size of MX-loaded spanlastics formulas.

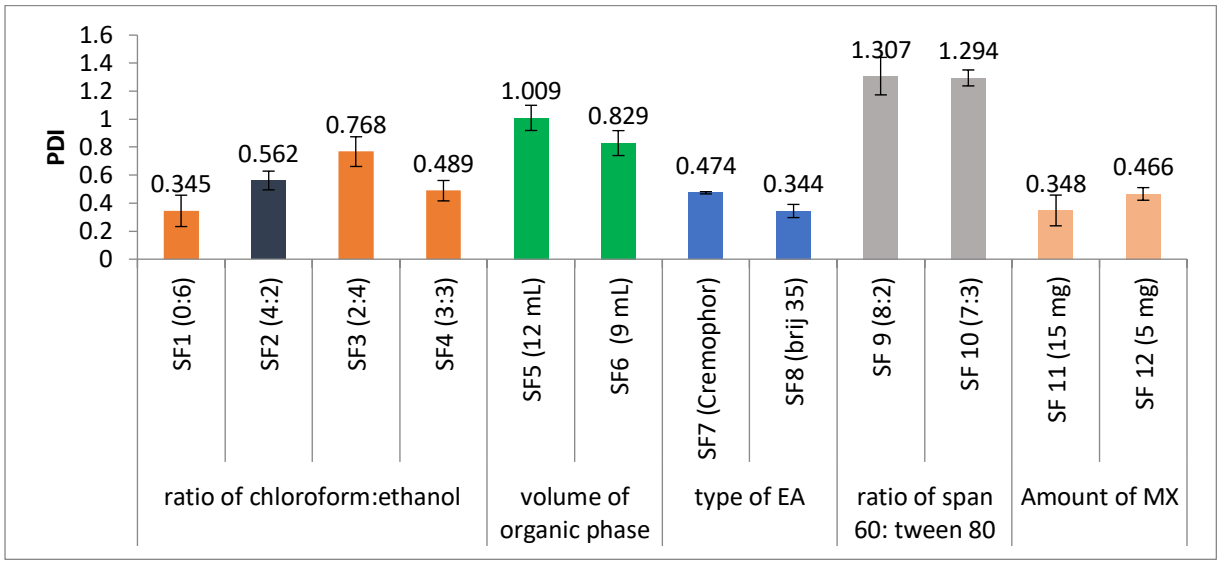

Figure3. The impact of formulation variables on the vesicular PDI of MX-loaded spanlastics formulas.

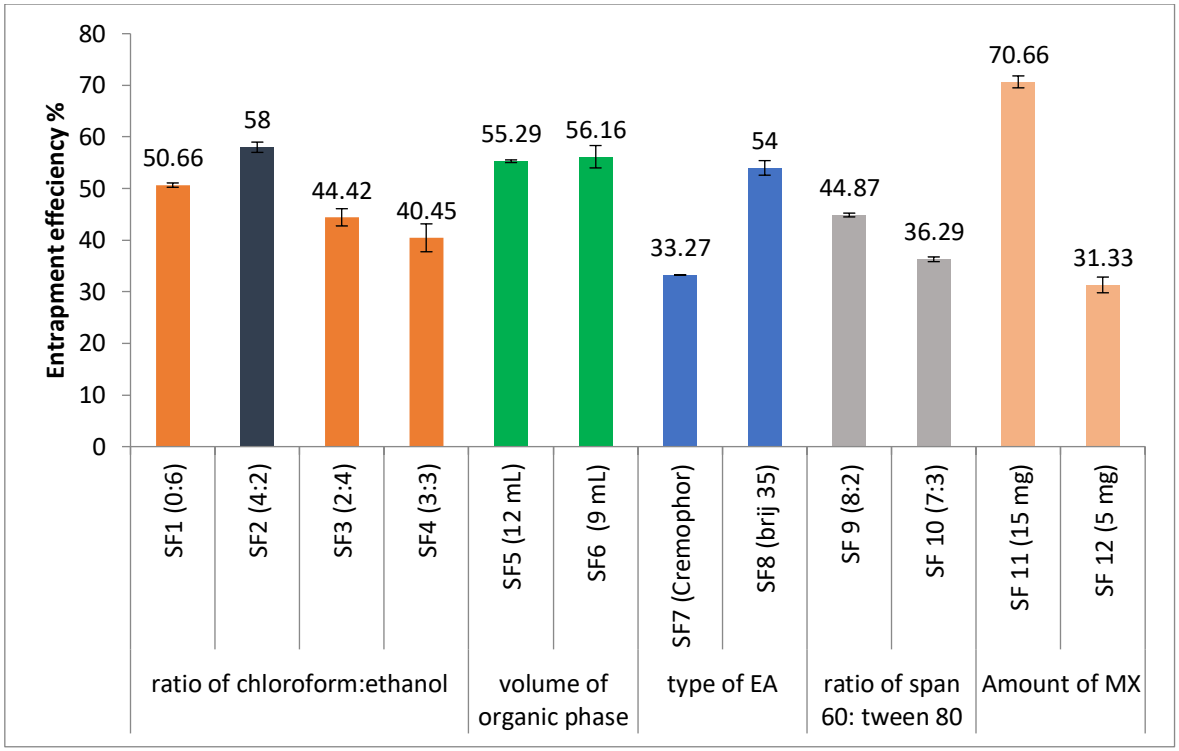

Figure 4. The percent entrapment efficiency of MX-loaded spanlastics formulas.

The effect of the type and volume of organic phase solvent

Regarding the effect of the type of organic phase solvent, keeping the same amount and composition of spanlastic formulas, data showed a significant difference ($p < 0.05$) in particle size, PDI, and EE% in the case of (SF1, SF2, SF3, and SF4). Despite, the effect of organic phase type and volume not being reported in the published spanlastics literature, there are only a few studies including this effect on properties of liposomes and niosomes which spanlastics are structurally similar except not containing phospholipid and cholesterol. The reason behind obtained results might be due to the differences in the polarity and viscosity of the organic solvent mixture used [20, 21]. Obeid *et al.* [21] reported that low-polarity organic solvent would be transformed upon mixing with an aqueous phase leading to a higher polarity gradient difference, while the viscosity of the organic phase affects the particle contact time and growth rate during the self-assembling process, these cause a significant difference in the characteristics of prepared noisome particularly when they loaded a hydrophobic drug.

On the other hand, the impact of increasing the organic phase volume to 12 and 9 mL in formulas (SF5 and SF6, respectively) compared to formula (SF2), was shown that when the organic phase's volume increased, the average particle diameter and PDI also increased ($p < 0.05$). This is due to as the organic volume raises, the amount of accessible emulsifier decrease, reducing the stabilizing effects of the produced vesicles.

The effect of the type of edge activator

Changing tween®80 in formula SF2 by cremophore®RH40 as edge activator in formula SF7 revealed significant ($p<0.05$) increasing in a vesicle size and decreasing in EE%. Meanwhile, using brij®35 (formula SF8) revealed a non-significant decrease in size or change in EE% with good dispersibility. These results were similar to that obtained by Mekkawy *et al.* [8] and they had been attributed to HLB values of edge activators, the smallest HLB value of tween 80 (HLB 14.5) and longest unsaturated alkyl chain C18 compared to the bulky branched structure of cremophore®RH40 and the shortest alkyl chain length of brij®35 with (C12) that may disrupt the integrity of membrane vesicles bilayer [22].

The effect of Span® 60: EA ratio

There is a statistically significant ($p <0.05$) increase in spanlastics size and reduce in EE% values when considering the change of the Span®60: EA ratio from 90:10 to 80:20 and 70:30 weight ratio for formulas SF2, SF9, and SF10, respectively. Tween®80 is the component added to soften the vesicular bilayer causing enhancement of permeation of the drug into vesicles by increasing bilayer flexibility. Furthermore, because of the hydrophilic nature of tween®80 surfactants, the vesicular membrane fluidization will be increased as increases of its amounts to a higher level and finally may account for the increased drug leakage to the surrounding aqueous phase. which would result in drug leakage thus lowering the EE% [23, 24]. That was in agreement with previous reports by the study of Nemer *et al.*[25] who found the largest vesicles

obtained at the highest EA ratio. Elsherif et al. [26] also stated that an increasing amount of tween®80 in their prepared spanlastic from 10% to 30% led to a lowering of EE% and it ranged between 40-60% which attributed to drug micellar solubilization induction in aqueous medium, thus lowered drug EE%.

The effect of the amount of drug

In studying the impact of increasing MX amount from 5 mg in formula SF12 to 10 mg for formula SF2 and 15 mg in formula SF11, it found a significant increase in EE% and vesicle size. This might be due to increasing the drug concentration in the media forcing the drug to encapsulate inside the vesicle layers, thus more drug entrapped led to larger vesicles and increased vesicle size. Similar findings were reported by previous research [8].

Release of MX-loaded spanlastics in vitro

The in-vitro release profile of pure MX suspension revealed higher drug release approximately 73% at 2 hours as illustrated in Figure 5, which considered rapid release in comparison with the selected MX-loaded spanlastics showed 55% and 47% for formulas SF2 and SF11, respectively. This could be a result of MX becoming trapped in the lipophilic area of the span® 60 bilayers which has a high transition temperature and a long chain length, in addition to tween®80, which results in the creation of a high-order semisolid state and impermeable bilayer, MX releases from spanlastics more slowly than it did from pure MX suspension [26].

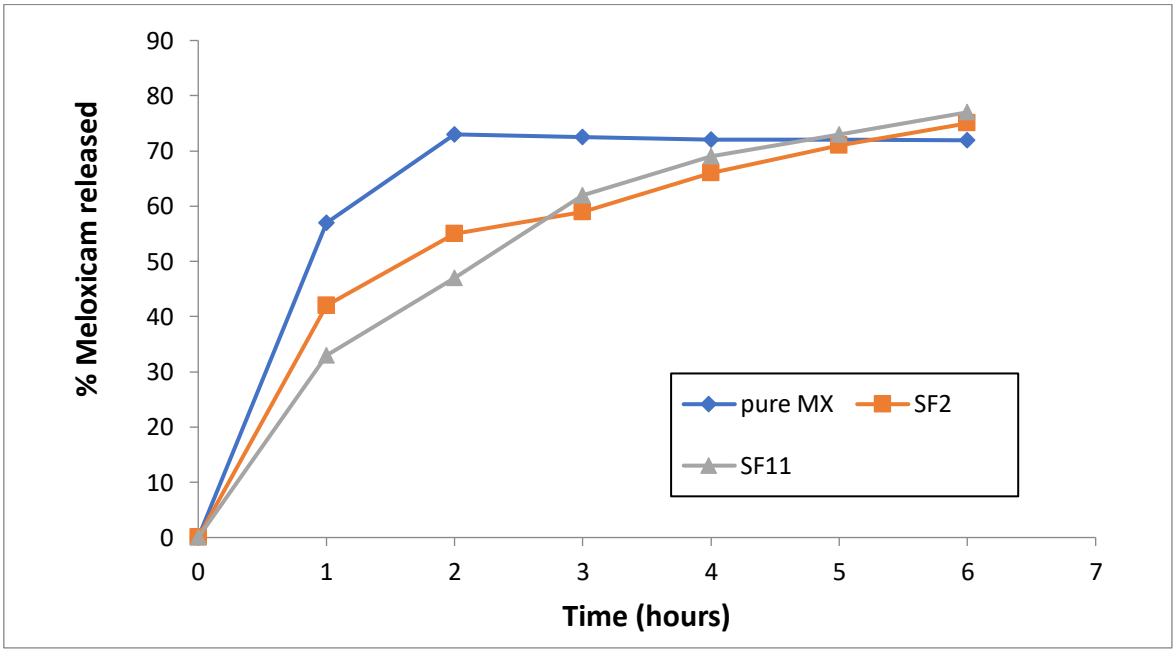

Figure 5. The released-time profile of pure meloxicam and loaded-spanlastics in phosphate buffer saline.

Modeling of release kinetic

The release of meloxicam from various spanlastics formulations was simulated using a variety of mathematical models. Table 2 listed the values of the regression coefficients and release constants.

Table 2. Data of In-vitro Meloxicam Released Kinetics

Formula code	Zero-order		First order		Higuchi model		Korsmeyer-Peppas model		
	K_0	R^2	K_1	R^2	kH	R^2	K_{kp}	n	R^2
SF2	15.363	0.5400	0.303	0.8765	33.164	0.9506	42.886	0.307	**0.9985**
SF11	15.560	0.7519	0.297	0.9726	33.176	0.9896	32.242	0.585	**0.9919**

The Korsmeyer-Peppas model was determined to be the best-fit model for understanding MX release from spanlastics formulations based on Table 2 since it had the highest R^2 values for all formulations that were tested. Similar results for drugs released from transfersomes have been reported by Khan *et al.* [27].

SF2 formula has the exponent (n value) less than 0.5 indicating that the drug transport mechanism is a close approximation to Fickian diffusion, whereas SF11 formula has the exponent (n value) more than 0.5 indicating that the drug transport mechanism is a close approximation to non-Fickian diffusion.

Based on the data of EE%, vesicle size, and PDI, the formula SF11 was selected as the optimum formula for further investigation.

Microscopic examination of formula SF11 in Figure 6 showed a homogeneous spherical shape with a thick membrane wall.

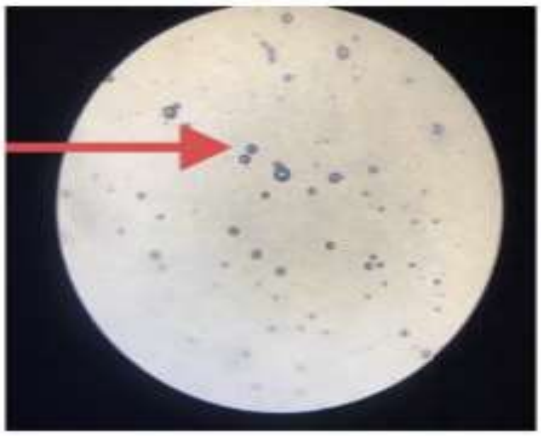

Figure 6. Optical microscope morphological study at 100X of formula SF11.

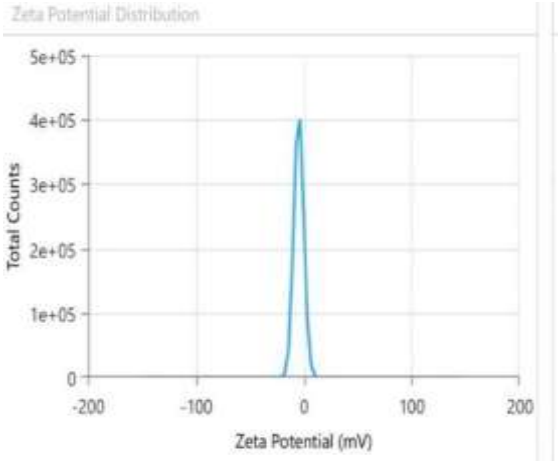

Figure 7. The zeta potential of the optimum MX-loaded spanlastics (SF11).

Zeta potential of the optimum MX-loaded spanlastics

The chosen MX-loaded spanlastic has a zeta potential of -4.51 mV as shown in Figure ٧, which was lower than reported values for electrostatics stabilization which may attributed to nonionic nature of surfactant used for spanlastics preparation that do not contribute any charge to the vesicles instead the colloidal vesicles would sterically stabilize by forming surfactant head coating around the vesicles surface and thus might reduce their interaction and aggregation by steric repulsion [28]. However, the obtained small negative zeta potential value was due to present of partial charged hydroxyl groups in the polar head of the nonionic surfactants [14, 23]. The trapping of meloxicam in the spanlastics vesicles the system is thought to be physically stable by steric effect. Ab Aziz and his coworkers achieved similar results and deduced that even their data showed low electrostatic stabilization, the prepared noisomes were homogenous with no phase separation and precipitation after storing for 60 days and furthermore, microscope images showed smooth dispersed spherical vesicles with non-aggregation [29].

FTIR spectrum of the optimum MX-loaded spanlastics formula

The FTIR spectra of pure meloxicam, span®60, tween®80, their physical combination, and the formula (SF11) of MX-loaded spanlastics are demonstrated in Figure 8. Pure meloxicam major bands are 3286.7, 1620.21, 1527.62, and 1184.29 cm^{-1} that is due to N-H stretching vibration, NH_2 scissoring vibration, C=N stretching vibration, and S=O stretching vibration, respectively. That was in agreement with previously published articles [9, 10, 30].

The (N-H stretching vibration) in the physical mixture's FTIR spectrum shows a minor shift from 3286.70 cm^{-1} to 3290.56 cm^{-1}, but the other major peaks show no changes. This shows that there is no interaction between meloxicam and the components used to make MX-loaded spanlastics.

Due to the trapping of meloxicam in the spanlastics vesicles, the FTIR spectrum of the SF11 optimum spanlastics formula of meloxicam lacks all of the major peaks of meloxicam, the same result is observed in celecoxib transethosomal gel [31].

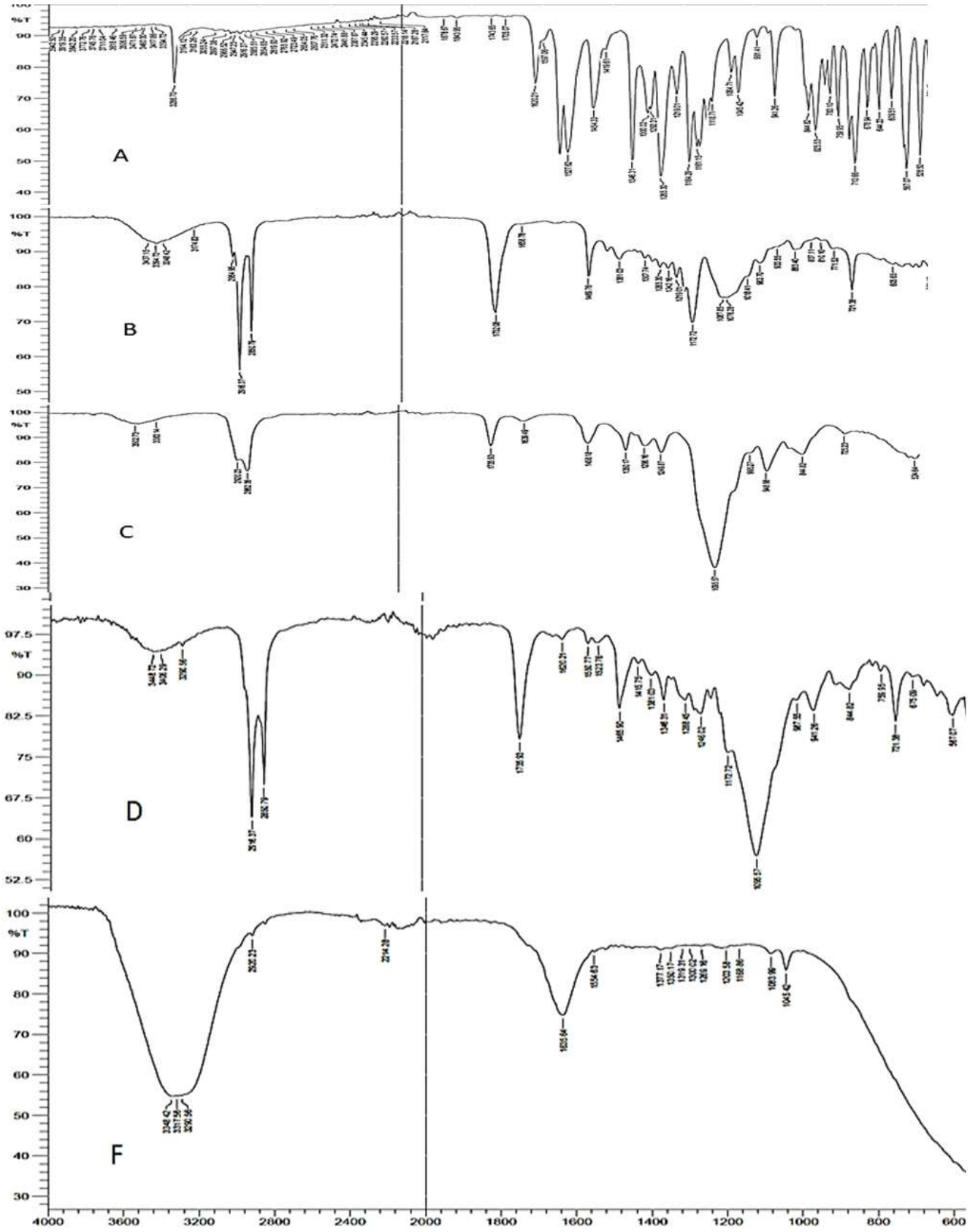

Figure 8. FTIR spectrum of meloxicam (A), span® 60 (B), Tween® 80 (C), physical combination (D), and MX-loaded spanlastics formula (F).

Conclusion

The study's conclusions show that the ratio of the span to the edge activators, the kind of edge

activators used, the dosage of the drug, and the kind and volume of organic phase solvent all had an impact on the efficiency of trapping, the size of the particles, and in the in-vitro release of the MX-loaded spanlastics. The selected formula (SF11) with the highest percent entrapment efficiency (70.66±1.15 %) and approved prolonged release were produced by the spanlastics made with span®60 and tween®80 at a weight ratio of (90:10) and chloroform to ethanol ratio of (4:2). Spanlastics can be used effectively for sustained delivery systems, according to the findings of the current study.

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Conflicts of Interest

We declare that there are no conflicts of interest.

Funding

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Ethics Statements

The research did not include any study on animal or human

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Lubna A.Sabri (L.A.S.); data collection: Mohammed Khalil (M.K.); analysis and interpretation of results: L.A.S, M.K.; draft manuscript preparation: L.A.S, M.K. All authors reviewed the results and approved the final version of the manuscript.

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تأثير تغييرعوامل الصيغة على تحضير ميلوكسيكام سبانلاستيكس

محمد خليل[١] و لبنى عبد الكريم صبري*[٢،]

[١] وزارة الصحة والبئية، دائرة صحة بابل، بابل، العراق.
[٢] فرع الصيدلانيات، كلية الصيدلة، جامعة بغداد، بغداد، العراق.

الخلاصة

سبانلستك هو نظام توصيل للدواء حديث يجمع بين الخصائص الحويصلية والجسيمات النانوية مع تمتعه بالعديد من المزايا مقارنة بالنظام الحويصلي التقليدي المستخدم موضعيًا من حيث الثبات ومرونة الاختراق والاستهداف. الميلوكسيكام هو دواء فعال مضاد للالتهابات غير الستيرويد يستخدم بشكل متكرر لعلاج الألم المزمن والأمراض الالتهابية بما في ذلك التهاب المفاصل الروماتويدي على المدى القصير اوالطويل . ومع ذلك ، فإن تناول ميلوكسيكام عن طريق الفم غالبًا ما يتضمن العديد من الآثار الضارة ، بما في ذلك الاضطرابات المعدية والمعوية والتقرح. وبالتالي ، فإن الهدف هو تحضير صيغة مناسبة من سبانلستك المحملة بـميلوكسيكام من خلال دراسة متغيرات الصياغة التي قد تؤثر على خصائصها باستخدام طريقة الحقن الإيثانول. المتغيرات تشمل ؛ نوع مذيب الطور الداخلي (ايثانول ,كلوروفورم) وحجمه, ونوع محفز المطاطية , ونسبة سبان ٦٠: محفز المطاطية وكمية الميلوكسيكام. تمت دراسة تأثيرالمتغيرات على حجم الجسيمات ومؤشر التشتت المتعدد وكفاءة الحصر. أظهرت الصيغة التي تم اختيارها إطلاقًا مستدامًا لمدة ست ساعات ، وجهد زيتا (- ٤,٥١ مليفولت) ، وكانت الجسيمات بحجم ٤٩٥ ± ٩,٩ نانومتر. بشكل عام ، أشارت النتائج إلى أن السبانلستك لديها القدرة على أن تكون حوامل لأنظمة توصيل للأدوية.

الكلمات المفتاحية: محفز المطاطية ,طريقة الحقن, ميلوكسيكام, سبان المطاطية, سبان ٦٠ .