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Preparation and Characterization of Prednisolone Acetate Microemulsion for Ophthalmic Use

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Abstract:

Background: Prednisolone acetate is an ester form of prednisolone. It is used topically as an ophthalmic suspension to treat many inflammatory ocular conditions, where its absorption from suspension is highly variable and has poor dose accuracy.

Objectives: The main objective of this research is to formulate and evaluate prednisolone acetate microemulsion for ophthalmic use to increase solubility, residence time, and corneal permeability of the drug to enhance patient compliance and treatment efficacy.

Methods: Twenty-four prednisolone acetate-loaded microemulsion (0.5%w/w) formulas were prepared using oleic acid, isopropyl myristate as (oil phase) (1:1), tween 80, labrasol, and cremophor EL as (surfactant), ethanol, polyethylene glycol 400, propylene glycol, transcutol P as co-surfactant and Sörensen isotonic phosphate buffer saline pH 7.4 as the aqueous phase at different Smix ratios (1:1), (1:2) and (2:1) by aqueous titration method to construct pseudoternary phase diagram to determine the existence of microemulsion region. All the prepared formulas were subjected to different evaluation tests to determine the optimum formula.

Results: observations of the microemulsion showed that it had a clear and transparent yellowish color, formulation F9 composed of oleic acid and isopropyl myristate in a ratio (1:1) as oil, twee80 as a surfactant, and propylene glycol: ethanol (1:1) in a ratio (2:1) as cosurfactant gave the best particle size (10.18nm), polydispersity index (0.2216), zeta potential (-25,91), % of transmittance (99.382%±0. 09), and drug content (100±0.16). Microemulsion formulation provided considerably higher permeability than the marketed eye drop suspension (Optipred®) and improved bioavailability.

Conclusions: The microemulsion-containing prednisolone acetate is a promising ocular carrier for the controlled release of prednisolone acetate in treating anterior segment inflammation.

Keywords: Atomic force microscopy, isopropyl myristate, microemulsion, oleic acid, prednisolone acetate.

Introduction

Eye drops as topical preparations are the most commonly preferred dosage forms for treating anterior segment eye diseases and represent a non-invasive route of administration (1–4). The concentration of the drug decreases rapidly upon eye drop instillation resulting in pulsating drug permeation (5, 6). The term "Microemulsion" (ME) is defined as the dispersion of water and oil in the presence of a surfactant and cosurfactant mixture (Smix) in a way that lowers interfacial tension and produces small particle sizes (5-200nm) with reduced surface tension. Microemulsion can enhance drug absorption via higher penetration and enhanced solubility (7-9). Prednisolone acetate (PA) is a synthetic version of the natural corticosteroid hormone produced by the adrenal gland, used to treat a wide range of conditions. Its effects include reducing pain, swelling, and allergic-type responses. (10-13). The highly lipophilic nature of the drug ester form and its poor aqueous solubility mandate a formulation to boost its permeability, solubility, and corneal contact time (14, 15).

Prednisolone acetate is commercially produced as an ophthalmic suspension in 1% micronized form and applied three to four times per day to achieve optimal therapeutic efficiency. Due to aggregation, sluggish dissolving rate, and limited corneal residence, medication absorption from suspension is highly variable and has poor dose accuracy (16). The present study aims to design ME systems for the ophthalmic delivery of the water-insoluble drug PA to enhance the solubility and increase the resident time and permeability of the drug.

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Materials and methods

Prednisolone Acetate (PA) purity of 99.4% purchased from Baoji Guokang Bio-Technology Co., Ltd. Isopropyl myristate (IPM), oleic acid, cremophore EL, transcutol P, labrasol and tween80(Tw80), were purchased from Taihua Bio.

Double deionized water (DDW) was prepared freshly whenever required.

Pre-formulation studies

Estimation of PA saturation solubility in various solutions:

The saturated solubility of PA was measured by adding an excess amount of PA powder to 5g of each oil, surfactant, co-surfactant, and dissolution media in firmly closed little glass tubes. To achieve equilibrium, the tubes were shaken in a thermostatically controlled shaking water bath at 25°C and 37°C for 72 hours (17,18). Samples were centrifuged, then the supernatants were removed, suitably diluted with methanol, and examined using a UV/Vis spectrophotometer at the λmax of PA.

Construction of pseudoternary phase diagrams:

The pseudoternary phase diagram was created by the aqueous titration technique following the findings of the solubility investigation. Origin 2018 graphing analysis was used in constructing these diagrams. Combining various surfactant and co-surfactant mixtures in ratios of 1:1, 1:2, and 2:1 was used based on expanding surfactant levels and rising co-surfactant concentration added to the oil phase which already contains the active pharmaceutical ingredient. Glass vials were used to combine selected oils with S-mix in varied ratios for each phase diagram (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) (w/w). The concentration of water in which the transition from clear to turbid happened was measured (19, 20).

Preparation of prednisolone acetate microemulsion

The primary emulsion was produced using the water titration method by dissolving 500mg of PA in the oil phase utilizing a vortex mixer for ten minutes, then adding the chosen S-mix in a predetermined quantity until a clear solution was obtained. The clear solution was then combined with the aqueous phase (Sorensen phosphate-buffered saline (SPBS)) while being continuously stirred at room temperature (750 rpm) using a magnetic stirrer, as illustrated in the table (1).

Table (1): Prednisolone acetate microemulsion composition

Formula No	Oleic acid & IPM (1:1) Oil w/w%	Surfactant: co-surfactant Smix	Smix ratio	Smix %w/w	SPBS %w/w	PA %w/w
F1	10	Tween80: Ethanol	1-1	35	55	0.5
F2	10	Tween80: Ethanol	1-2	30	60	0.5
F3	10	Tween80: Ethanol	2-1	30	60	0.5
F4	10	Tween80:PEG400	1-1	55	35	0.5
F5	10	Tween80:PEG400	1-2	65	25	0.5
F6	10	Tween80:PEG400	2-1	60	30	0.5
F7	10	Tween80: Ethanol	1-1	35	55	0.5
F8	10	Tween80:PG/Ethanol	1-2	30	60	0.5
F9	10	Tween80:PG/Ethanol	2-1	30	60	0.5
F10	10	Tween80: Transcutol P	1-1	40	50	0.5
F11	10	Tween80: Transcutol P	1-2	35	55	0.5
F12	10	Tween80: Transcutol P	2-1	30	60	0.5
F13	10	Labrasol: Transcutol P	1-1	60	30	0.5
F14	10	Labrasol: Transcutol P	1-2	55	35	0.5
F15	10	Labrasol: Transcutol P	2-1	35	55	0.5
F16	10	Cremophor EL: Transcutol P	1-1	55	35	0.5
F17	10	Cremophor EL: Transcutol P	1-2	55	35	0.5
F18	10	Cremophor EL: Transcutol P	2-1	60	30	0.5
F19	20	Tween80: Ethanol	2-1	40	40	0.5
F20	20	Tween80:PEG400	2-1	60	20	0.5
F21	20	Tween80:PG/Ethanol	2-1	40	40	0.5
F22	20	Tween80: Transcutol P	1-2	30	60	0.5
F23	20	Labrasol: Transcutol P	2-1	30	60	0.5
F24	20	Cremophor EL: Transcutol P	1-1	40	50	0.5

Characterization of prepared prednisolone acetate microemulsion

Investigating the thermodynamic stability

To test the optimized formulation thermodynamic stability, the prepared MEs were subjected to a 30-minute centrifugation at 6000rpm to check for phase separation, creaming, and cracking. A heating-cooling cycle exposed the prepared ME to 40°C and 4°C alternately for less than 48 hours. Finally, they were subjected to three freeze-thaw cycles between -21°C and +25°C with storage at each temperature for about 48 hours (21).

Measurement of light transmission (%T): For each of the prepared ME the percentage of light transmittance was measured. Measurements were made by using a UV-vis spectrophotometer set to 650 nm and distilled water was used as a control (22,23)

Determining particle size, polydispersity index, and zeta potential: The particle size and zeta potential were determined using the Malvern panalytical particle size analyzer, which also provides other options such as assessing an average diameter and calculating the polydispersity (24,25).

Drug content estimation

The amount of PA in prepared MEs was determined using a UV spectroscopic approach. A mass weighing 1 g (containing 5mg of PA) of ME was dissolved in methanol and then analyzed at 242 nm in the UV-visible spectrophotometer (26).

Characterizing the selected prednisolone acetate microemulsion

Determination of osmolality

Ex-vivo permeation study: Fresh sheep corneal membrane tissues were carefully taken from a sheep procured from a local slaughterhouse. It was carefully removed and immersed in an SPBS until it is used for the research. For the ex-vivo study, the corneal membrane was put on Franz diffusion cell type b (closed/occluded mode) with capacity (7ml) and the external side facing the donor compartment (28).

The ME formula equivalent to 4mg of PA was put in the donor compartment. At predetermined intervals, 1ml sample from the receptor chamber was taken at 50 rpm and 34 C˚. After each sampling, the sampled volume was replaced with fresh media. The withdrawn samples were used for analysis by UV-VIS spectrophotometer to quantify the amount of drug that permeates through the cornea.

Test for ocular irritation: Six rabbits were split into two separate groups (three rabbits each, n = 3), with group I receiving drug suspension and group II receiving the selected microemulsion. An aliquot of 50µl (0.5% w/v PA) of the tested formulation was placed in the right eye conjunctival sac only, leaving the left eye as a control. Both eyes were checked for inflammation symptoms such as redness, increased lacrimation, conjunctival edema, and hyperemia. The animals were examined after 2, 4, 6, 8, 24, and 48 hours (25).

Morphological visualization by atomic force microscope (AFM)

The atomic force microscope is a relatively new technique that is being used to investigate the surface morphology of ME formulations these days (29).

Results

Saturation solubility of prednisolone acetate

Solubility of PA was screened in different oils, and among tested oils, isopropyl myristate (IPM) and oleic acid exhibit higher solubilizing capacity when used in combination together in a ratio (1:1) than oleic acid or IPM alone as shown in figure (1).

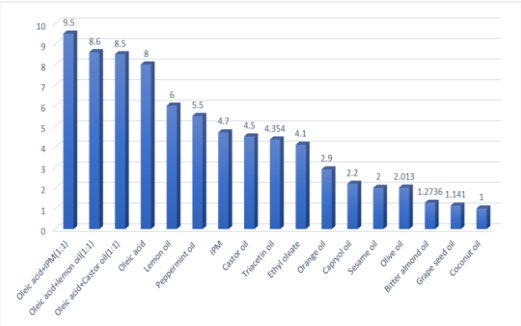

Figure (1): Saturated solubility of PA in different oils.

Three surfactants were used to prepare the surfactant/co-surfactant mixture or Smix in the study, namely tween 80(Tw80), cremophor EL(CremEL), and labrasol(Lab), furthermore, propylene glycol (PG), ethanol (EtOH), polyethyleneglycol 400(PEG400), and transcutol P (Trans P) as cosurfactant as those show the greater solubility for PA.

The osmolarity was measured by using a 5004-micro-osmette-automatic high sensitivity 50 µL osmometer (Precision Systems Inc, USA) (27).

Pseudoternary phase diagram

The largest shaded area that represents the MEs, as illustrated in figure (2), that is clear in the micro-sized is the formulas that contain Tw80 as a surfactant and PG: EtOH (1:1) as co-surfactant(22).

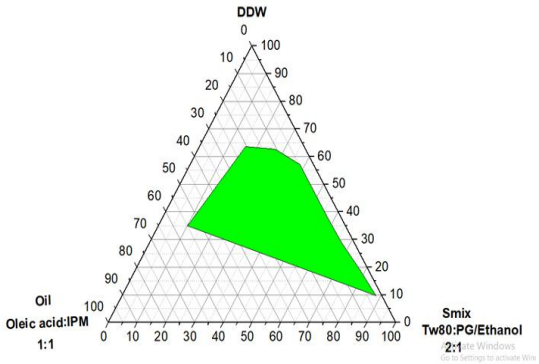

Figure (2): Pseudoternary phase diagrams showing the (o/w) microemulsions (shaded area)

Characterization of the prepared PA MEs

Thermodynamic stability study

According to the results, the formed MEs were thermodynamically and physically stable systems, except for the formula (F1) that showed precipitation (30).

Percentage light transmittance (T %): The results with a percentage transmittance value closer to 100 percent, as Table (2) displays, demonstrate that each one of the best formulations was clear and transparent since decreasing droplet size to the nanoscale led to increased transparency (31).

Particle size, polydispersity index, and zeta potential results: The result revealed the largest average droplet size found in formulas (F19- F24), as shown in Table (2). The smallest particle size found in formula number (9) contains Teen80 as a surfactant and propylene glycol: ethanol (2:1) as a co-surfactant (32).

The polydispersity index of the qualified MEs formulas was in the range of (0.002-0.87) as seen in the table (2), so it is in the limited range from 0.0 to 1.0, indicating a uniform and narrow globule size distribution, stability (33). Zeta potential is utilized as an indirect measurement of a particle surface charge density; thus, it is considered a significant metric and gives an inverse relationship between colloidal particles and agglomeration propensity that can be examined (34). The optimum particle size of the prepared ME formulas, which have been below 200 nm, was chosen for further studies.

Table (2): Particle size measurement and polydispersity index (PDI), zeta potential, %transmittance and drug content of PA MEs

No. of Formula	Particle size(nm)	PDI	Zeta potential	%Transmittance Mean± SD (n=3)	Drug content (%) Mean± SD (n=3)
F2	125.1	0.2398	-20.59	98.9±0.11	100.08±0.18
F3	36.29	0.1568	-26.49	99.28±0.08	99.64±0.12
F4	212	0.8498		98.85±0.02	100±0.19
F5	358.2	0.2334		99.31±0.03	100±0.17
F6	138.4	0.513	-44.3	97.05±0.14	94.18±0.12
F7	210.3	0.04137		98.174±0.03	100±0.14
F8	121.7	0.2436	-24.42	93.97±0.51	99.23±0.21
F9	10.18	0.2216	-25.91	99.382±0.09	100±0.16
F10	298.8	0.3066		97.723±0.08	97.02±0.18
F11	369.4	0.3518	-11.48	93.325±0.06	92.665±0.16
F12	69.3	0.4711	-20.03	98.855±0.05	100±0.19
F13	323.7	0.5261		99.08±0.01	100±0.150
F14	165.2	0.2908	-34.51	97.05±0.02	100.67±0.16
F15	174.8	0.1107	-30.47	95.4±0.07	99.84±0.14
F16	303.7	0.2563		97.948±0.024	100.20±0.17
F17	196.4	0.3529	-42.1	97.723±0.03	100.73±0.11
F18	229.7	0.2959		96.4±0.12	99.257±0.20
F19	467.3	0.4822			
F20	888	0.871			
F21	484.4	0.6164			
F22	487.2	0.5568			
F23	770.2	0.002			
F24	833.8	0.4267			

Microemulsion drug content: All the prepared PA MEs formulas agreed upon in accordance with the British Pharmacopea (BP) range requirements, as results shown in table (2), that indicates the method of preparation is adequate, and every formula has high content uniformity (35).

Osmolarity: The result osmolarity of the optimum formula F9, which had the finest particle size, was found to be 282± 1, which is within the accepted value, preventing any irritation (36).

Ex-vivo permeation of PA microemulsion: The optimum formula F9 was most efficient in permeating the drug through the eye cornea, as shown in Figure (3). The results are based on the cumulative amount permeated per unit area values, steady state flux, and permeability coefficient F9 and PA suspension. Fluxes were (7.514 ±0.092 ug/cm2.min) and (3.0075±0.15 ug/cm2.min) respectively. PA permeability coefficient increased by 2.49-fold in the case of F9 (1.87*10-3± 0.85cm/s) in comparison with the permeability coefficient of PA suspension (0.75*10-3 ± 0.23cm/s).

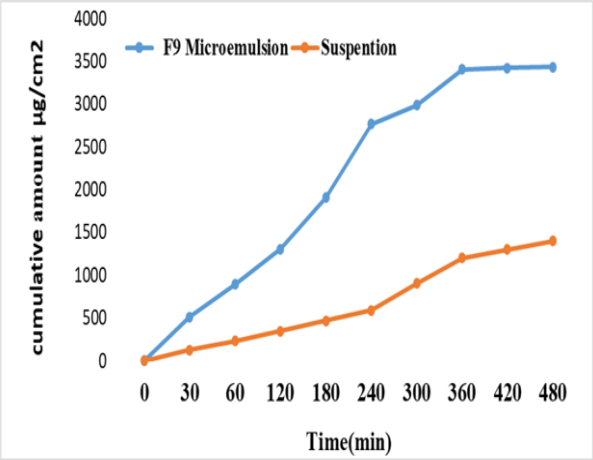

Figure (3): PA permeation through sheep corneas from F9 ME and PA suspension.

Irritation test

The irritation check results revealed that the chosen ME did not cause any sign of inflammation, which may be attributed to the use of a low concentration of Smix, as well as its safe and not irritant. furthermore, the aqueous media used in MEs formulation was the SPBS pH 7.4, characterized by pH and osmolality same as the human tears (37).

Atomic force microscopy (AFM): Atomic force microscopy was used as an additional technique to clarify that the particle size and surface of the developed emulsion is in the nano range, enhancing drug delivery, as illustrated in Figure (4).

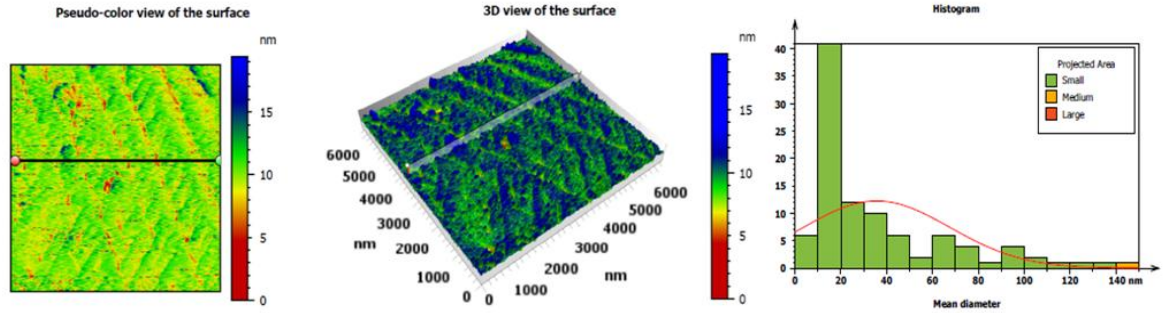

Figure (4): (A) The AFM image, (B)The AFM 3D of PA ME (C) Histogram of Surface Texture of PA ME by AFM

Discussion

The results of this study demonstrated that all the prepared microemulsion formulations were stable, except for (F1). The reason for this was that in order to achieve thermodynamic stability, the amount of (tween80: ethanol) ratio (1:1) used as a surfactant-cosurfactant should be greater than 39%; however, this formula only used 30% of that amount in order to reduce the risk of ocular toxicity. The particle size finding displayed that as the oil concentration increased, the average droplet size increased as in formulas(F18-F24). This can be attributed to the expansion of the oil drop of the microemulsion caused by the addition of more oil. When the surfactant concentration was increased, the emulsion droplet size decreased. This is because there is more surfactant present to cover any new droplet surfaces formed during preparation. The osmotic pressure was approximately identical to that of people., due to the sodium chloride used in the SPBS in a concentration to reach the osmolarity near the human tears. Furthermore, PG was used as osmotic pressure management in ophthalmic preparation (35). The difference in the amount permeated between the formulas and control suspension could be attributed to the fact that this small and uniform droplet size is critical for achieving high corneal penetration. In addition, the presence of oleic acid, Tw80, PG, and ethanol can promote better membrane permeability by acting as a lipophilic permeation enhancer. the result indicates a higher permeation and flux for MEs formulas in comparison to the control.

Conclusion

From this study, it is concluded that the PA-ME containing 10% oleic acid and IPM, 30% Tw80:PG/ethanol, and 60% SPBS showed good thermodynamic stability and a globule size in the nano-metric range. The new dosage form showed enhanced in-vitro drug release profiles compared with generic ophthalmic suspension, which confirms the enhancing characteristics of the ME components and provides a potential for higher absorption and bioavailability.

Authors' contributions:
Reem A Al-Rubaye: Student
Khalid K Al-Kinani: Supervisor

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تحضير وتوصيف مستحلب اسيتات البريدنيزولون للاستخدام في العين

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خلفية البحث: اسيتات البريدنيزولون هو على شكل استرمن البريدنيزولون، يستخدم موضعياً كمعلق عيني لعلاج الكثير من حالات التهاب العين، حيث يكون امتصاصه من المعلق متغيرًا بدرجة عالية ولديه دقة جرعة ضعيفة. الاهداف: الهدف الرئيسي من هذا البحث هو صياغة وتقييم المستحلب الدقيق لأسيتات البريدنيزولون للاستخدام في العين لزيادة قابلية الذوبان، ووقت الإقامة، ونفاذية الدواء في القرنية لتعزيز امتثال المريض وفعالية العلاج.
طرق العمل: تم تحضير أربعة وعشرين صيغة من المستحلبات الدقيقة المحملة بأسيتات البريدنيزولون (0.5٪ وزن / وزن) باستخدام حمض الأوليك ، آيزوبروبيل ميريستات) (IPM) كطور زيتي) (1: 1) ، توين 80 (Tw80) ، لابراسول ، كريموفور (كخافض للتوتر السطحي) ، إيثانول ، بولي إيثيلين جلايكولPEG400 ، بروبيلين جليكول (PG) ، ترانس كوتول P كخافض للتوتر السطحي ومنظم فوسفاتي للسورينسين متساوي التوتر Sörensen (SPBS) درجة الحموضة 7.4 كطور مائي بنسب مختلفة من Smix (1: 1) ، (2: 1)و(1: 2) بطريقة المعايرة المائية لإنشاء مخطط طور كاذب لتحديد وجود منطقة مستحلب دقيق. تم إخضاع جميع الصيغ المعدة لاختبارات تقييم مختلفة لتحديد الصيغة المثلى.
النتائج: أظهرت ملاحظات المستحلب الدقيق أن هناك الصيغة F9 ذات لون مصفرواضح وشفاف، حيث تتكون من حمض الأوليك و IPMبنسبة (1: 1) كزيت، و Tw80على شكل خافض للتوتر السطحي، و PG: EtOH (1: 1)بنسبة (2: 1) حيث أعطى العامل المساعد الخافض للتوتر السطحي أفضل حجم جسيم (10.18 نانومتر)، مؤشر التشتت المتعدد (0.2216)، جهد زيتا (-25.91)، نسبة النفاذية (0.9±٪ 99.382)، محتوى الدواء (0.16 ±100)، وإصدار النتائج بعد 8 ساعات (100%). قدمت تركيبة المستحلبات الدقيقة نفاذية اعلى من معلق قطرات العين المسوق (Optipred®)وتحسين التوافر البيولوجي.
الاستنتاجات: تشير نتائج البحث إلى أن تركيبة المستحلبات الدقيقة المحتويه على اسيتات البريدنيزولون هو ناقل عيني واعد للإفراز الخاضع للرقابة من اسيتات البريدنيزولون في علاج التهاب الجزء الأمامي من العين.
الكلمات المفتاحية: مستحلب دقيق، اسيتات البريدنيزولون، حمض الأوليك، قياس حجم الجسيمات، اختبار تهيج العين، ودراسة نفاذية خارج الجسم الحي.