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PREPARATION, CHARACTERIZATION AND *EX-VIVO* HUMAN SKIN PERMEATION OF IBUPROFEN-SOLUPLUS POLYMERIC NANOMICELLES

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ABSTRACT: Ibuprofen is a widely used non-selective non-steroidal anti-inflammatory drug. Ibuprofen oral use is restricted by its potential gastric toxicity, which can be overcome utilizing alternative drug delivery routes. A novel micellar transdermal delivery of Ibuprofen was readily prepared herein using the solubility enhancing co-polymeric excipient polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®). Ibuprofen polymeric micelle systems were prepared at a wide range of concentrations and characterized by particle size analysis, rheology measurement, infrared spectroscopy, and differential scanning calorimetry. Nanosize micelles were obtained (< 100 nm), with a small polydispersity index, at 0.5 – 2% concentration range of Soluplus®. The aqueous solubility of Ibuprofen was significantly enhanced in Soluplus®micelle system. The highest solubility was achieved at a concentration of 2% of Soluplus® with an approximate ten-fold increase in solubility. Moreover, statistical analysis of Ibuprofen's permeation from Ibuprofen polymeric micelle systems against a control sample revealed an increase in the cumulative drug permeation with increasing polymer concentration.

INTRODUCTION: Ibuprofen (IBU) is a lipophilic non-steroidal anti-inflammatory drug (NSAID) with low aqueous solubility that is commonly used in the management of various types of inflammatory diseases (*i.e.*, rheumatoid osteoarthritis, ankylosing spondylitis, gout and Barrett's syndrome) [1, 2]. Being a non-selective NSAID, IBU is known for its potential to cause both localized and systemic gastric toxicity [3].

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Furthermore, IBU has a relatively short half-life, and multiple doses have to be administered to maintain its pharmacological effect [4, 5]. Multiple dosing of the drug further increases the risk of gastric toxicity signs like irritation, bleeding, abdominal pain and ulcers.

Transdermal delivery of IBU may be considered an alternative route of administration to circumvent the local gastric toxicity in situations requiring frequent dosing [6, 7]. The primary challenge in transdermal drug delivery is the stratum corneum (SC). Being the outermost layer of the skin, the SC serves as a protective barrier to prevent the absorption of elements of the environment into the body. Besides, SC creates a barrier that a successful transdermal formulation has to overcome to

achieve and maintain therapeutically significant concentrations of the drug in the body [8]. Several approaches to circumvent the SC and enhance drug permeation through the skin were investigated, such as; eutectic mixtures, nanoemulsions, iontophoresis, sonospheres, permeation enhancers, and polymeric nanomicelles [9-13]. Polymeric nano-micelles have been the subject of limited transdermal testing. Those systems permeate into the lipidic space between corneocytes due to their small size, effectively bypassing the SC.

A novel, amphiphilic, highly water-soluble, caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) (SP) has been recently introduced as a dissolution and absorption enhancer for poorly water-soluble APIs. The copolymer has been investigated for its ability to produce glass solutions *via* hot-melt extrusion (HME). Moreover, SP has an exciting property regarding its ability to form polymeric micelle structure in solution [14, 15].

Polymeric micelles as drug vehicles have made rapid progress during the last two decades, and several formulations are already being evaluated in late-stage clinical trials [16]. However, SP's use for the creation of polymeric micelle for transdermal delivery remains mostly unexplored [17, 18]. In the present work, SP was used to produce a nano-sized polymeric micelle system of IBU for transdermal delivery. The described system employs a simple method of preparation and was tested using human skin permeation studies.

MATERIALS AND METHODS:

Materials: Soluplus® was obtained as a generous gift from TQ Pharma, Jordan. IBU was obtained from the Jordanian Pharmaceutical Manufacturing Co. PLC., Jordan. Absolute ethanol (≥99.8% GC) was purchased from Sigma Aldrich. Any other reagents used in this study were analytical and/or HPLC grades.

Methods:

Preparation of the IBU-Soluplus® Polymeric Micelles: Aqueous dispersions of SP were prepared at varying concentrations (0.004%, 0.008%, 0.016%, 0.125%, 0.25%, 0.5%, 1.0% and 2.0% w/v) to obtain a volume of 10 ml for each sample. IBU was dissolved in absolute ethanol to obtain a concentration of 1.0 g/ml. A volume of 0.1 ml of IBU-ethanol solution was added gradually to each SP aqueous dispersion concentration, using a graduated plastic syringe. The samples were vigorously mixed using a vortex mixer (Baxter Scientific SP S8223) at 2000 rpm for 3 min at room temperature.

Determination of Particle Size and Poly-dispersity Index: Particle size and poly-dispersity index (PDI) measurements were carried out using a Nano ZS Zetasizer (Malvern Instruments, UK) at 20 ºC. Measurements were conducted in triplicates; the results were reported as the mean values ± Standard Deviation (SD).

Solubility Study: Three aqueous dispersions (100 ml each) of the co-polymer SP (0.25%, 1% and 2% w/v) were prepared. To each of the three aqueous dispersions, an excess amount of IBU (~1 g) was added at 32 °C (skin temperature) and kept in a thermostatic shaking water bath (Shanghai Boxun Medical Equipment Plant, China) for 48 h. The samples were centrifuged in a Beckman JA-10 rotor for 20 min at 8000 rpm. The clear, supernatant solutions were analyzed by HPLC; each analysis was done in triplicates; the results were reported as the mean values ± standard deviation.

Viscosity Measurements: The viscosity measure-ments of the copolymer 2% w/v aqueous solution and the Ibuprofen polymeric micelle systems(IBU-PMs) 2% w/v were carried out using a plate rheometer (Bohlin CVO Rheometer with Peltier, Malvern, UK). The measurements were taken at a set temperature of 25 ºC, with the table of shears between 0.1 and 240 (1/S), down and up mode, CP 4º/40 mm plate, delay, and integration times of 5 s and a gap size of 150 µm. The effect of the temperature gradient on viscosity was also assessed. The thermal parameters were as follows: thermal equilibrium time of 30 s, the temperature gradient of 25-50 ºC, and a heating rate of 6 ºC/min.

Infrared spectroscopy (FTIR) and Thermal Testing (DSC): IBU-PMs (with a ratio of 0.1:2 w/w) were centrifuged at 15,000 RPM for 30 minutes. The precipitate was dried in an oven at 35 ºC for 25 h before the analysis. Separate ethanolic

solutions of IBU and the copolymer were dried under similar conditions. The dry samples were mounted on a flat piece on the DSR 8000A accessory of the Prestige-21 FTIR (Shimadzu, Japam). DSC analysis was carried out using a DSC 823; model SMP/PE 7548/MET 400 Watt (Artsyn Technologies, Switzerland) with a heating rate of 10 ºC in the 25-250 ºC temperature range.

Permeation Study:

Preparation of the Epidermis: Full-thickness abdominal human skin was obtained from a 42 years old female who had undergone cosmetic surgery. This was reviewed and approved in advance by the Ethical Committee of the Human Investigation Review Board at the University of Petra (approval number 8/4/2017). Upon surgical removal from the body, the skin was immediately transferred to the lab in an ice bag. The adhered subcutaneous tissue was surgically removed using forceps.

Skin samples were washed several times using a phosphate buffer solution (PBS) of pH 7.2, then mounted on a hard surface and wrapped with aluminum foil, then sealed in evacuated polyethylene bags and stored at -60 ºC for no longer than three months [19].

For the *ex-vivo* permeation study, the frozen skin samples were cut to appropriate size then thawed at room temperature before the experiment. Skin samples were rehydrated using PBS of pH 7.2. The epidermis layer was separated from the dermis tissue using the heat-separation procedure (20). Briefly, the skin samples were immersed in a water bath at 60 ºC for one minute.

After that, skin samples were placed on a filter paper, siding up the stratum corneum. The epidermis was gently peeled using forceps from the underlying dermis. The separated epidermis membrane was then floated onto the water, and it was placed on supporting cellulose acetate membrane (pore size: 0.45 mm, Porafil, Machenerey-Nagel, Düren, Germany and Pall Life Sciences, Washington, NY, USA).

***Ex-vivo* Skin Permeation Studies:** The epidermis samples were floated in the water, thoroughly blotted over a filter paper, then transferred to a jacketed Franz diffusion cell (diffusion area = 1.77 cm^2, receptor volume = 15 ml). PBS of pH 7.2 was used as a receptor fluid. The system was maintained in constant agitation using a Teflon-coated magnetic stirrer at 600 rpm. The epidermis samples were allowed to hydrate for one hour before the diffusion run [15]. A quantity of 1.5 ml of 0.25%, 1%, or 2% of IBU-PMs (3.75, 15, 30 mg IBU respectively) against a control sample (1.5 ml of 2% IBU aqueous suspension containing no SP). Samples (1.0 ml) were taken from the receptor solution at specific time points up to 30 h; the withdrawn samples were immediately replenished with fresh medium to maintain sink conditions. The receptor solution sample's drug content was analyzed using an HPLC method described by Badwan and Al-Remawi [21]. The results are denoted as mean ± standard deviation of all three experiments. The cumulative amount of the permeated drug was plotted versus time.

Statistical Analysis: Statistical analysis of the data was carried out using SPSS statistical analysis suite version 16 (IBM Analytics, Chicago, IL). A one-way ANOVA test was used to determine the statistical significance ($P<0.05$) of the difference between the tested formulations.

RESULTS AND DISCUSSION:

Characterization of the IBU-PMs: Because of its amphiphilic nature, SP molecules, above a critical concentration (CMC) of 0.8 mg/mL [22, 15], self-aggregate in aqueous solutions to form spherical micelles and as a consequence, the solubility of poorly water-soluble drugs can be greatly enhanced. In the present work, all tested SP dispersions (0.004% - 2.0 % w/v) were above the CMC. For the estimation of the size of the micelles and the polydispersity, dynamic light scattering was used. The Z-average is interpreted as the micelle's hydrodynamic diameter, and the PDI for the tested SP dispersions are shown in **Fig. 1** and **2**. As shown, pure SP had an average micelle size of approximately 60–80 nm and a PDI between 0.08 and 0.4; this indicated a homogeneous population of the formed micelles with a monophasic size distribution, which looks very similar to a previously reported reading [23]. With respect to IBU-PMs, nano-sized micelles were obtained for SP aqueous dispersions (at a concentration range from 0.5 to 2.0 % w/w).

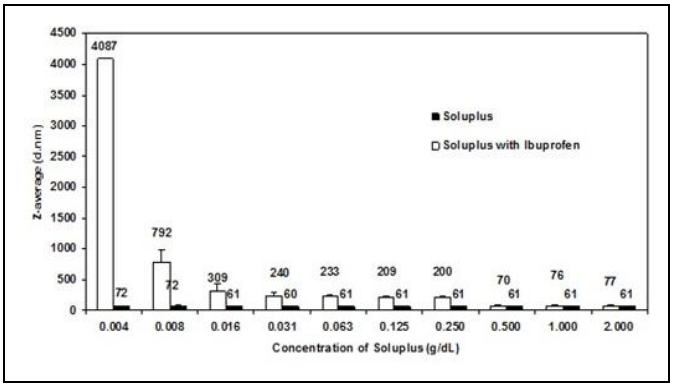

FIG. 1: THE PARTICLE SIZE OF CO-POLYMER AND IBUPROFEN CO-POLYMER NANOMIECLLES AT DIFFERENT COPOLYMER CONCENTRATIONS

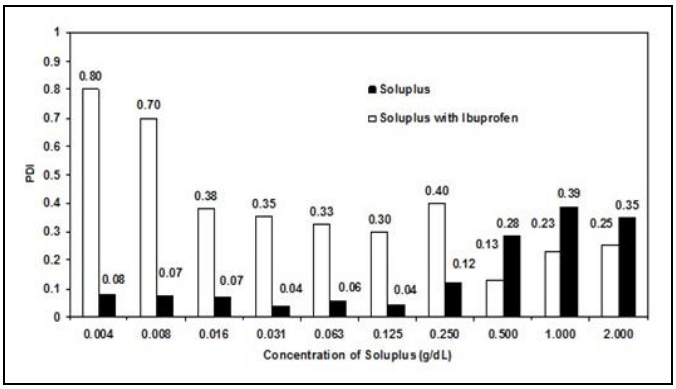

FIG. 2: PDI OF CO-POLYMER AND IBUPROFEN CO-POLYMER NANOMIECLLES AT DIFFERENT COPOLYMER CONCENTRATIONS

A water solubility of approximately 0.106 mg/ml at 32 °C was obtained for IBU, which is higher than those reported at 25 °C (0.09 mg/mL [24, 25], 0.060 mg/ml [26] and 0.081 mg/mL [27]) but comparable to the reported solubility value of 0.110 mg/ml at 32 °C [28]. PMs significantly enhanced IBU solubility due to micelle solubilization. The highest solubility was achieved at 2% SP concentration with an approximate ten-fold increase in solubility.

Regarding the viscosity, the dependency of pure SP and IBU-PMs viscosities on the shear rate is exhibited in **Fig. 3**. It is evident from **Fig. 3** that as the shear rate increases, the viscosity decreases until reaching solvent viscosity ($H_2O \approx 1.0$ m Pa.s) at high shear rates ($\geq 10\ s^{-1}$). Such behavior is called shear-thinning. It is also apparent from Fig. 3 that at low shear rates, the viscosity of IBU-PMs dispersions is higher than that of pure SP, which could be due to the physical interaction between the drug and the surfactant. At higher shear rates, the interaction between IBU and SP vanishes due to the strong shear. As a result, the viscosities of both dispersions become similar to that of water, which could explain the system's thixotropic behavior [29]. A hydrophobic drug may also stabilize the micelle through additional hydrophobic interactions between the drug and the hydrophobic part of the micelles [30]. Such interaction may explain the higher viscosity of IBU-PMs.

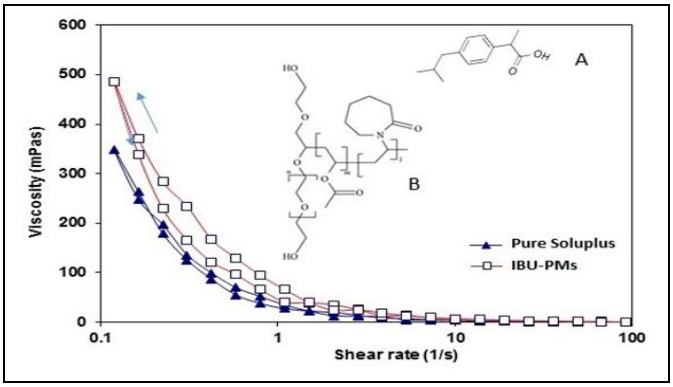

FIG. 3: VISCOSITY AND SHEAR RATE OF CO-POLYMER AND IBUPROFEN CO-POLYMER NANOMIECLLES MEASURED AT DIFFERENT SHEAR RATES. THE CHEMICAL STRUCTURES OF IBUPROFEN AND CO-POLYMER ARE INCLUDED AS A AND B, RESPECTIVELY

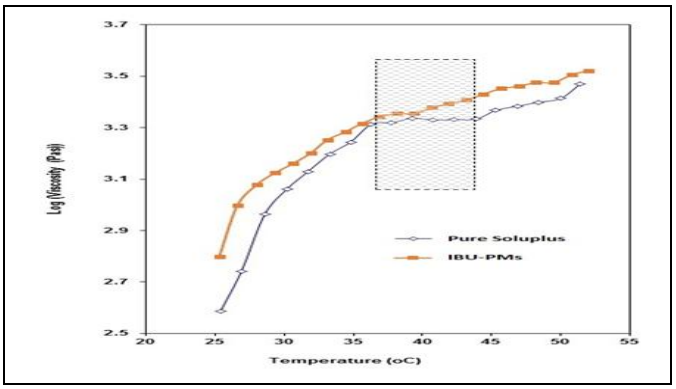

FIG. 4: THE VISCOSITY OF CO-POLYMER AND IBUPROFEN CO-POLYMER NANOMIECLLES UPON TEMPERATURE CHANGE AT A CONSTANT SHEAR RATE (0.1 S-1). THE SHADED AREA IS THE TRANSITION AREA

In the literature, the viscosity of SP was investigated concerning the temperature. These studies were conducted at high polymer concentration, shear rates and temperature to study the gelling behavior [31]. In the present study, the change in viscosity of SP and IBU-PMs against a temperature range of 25 - 50 °C and a slow shear rate (0.1 S-1) was studied. The results obtained **Fig. 4** showed an increase in the pure SP and the IBU-PM's dispersion viscosity with increasing temperature. This unusual increase in viscosity with temperature was previously reported for PEG-based, non-ionic, polymeric surfactants. Surfactants

such as polyethylene phytosteryl ether, polyoxy-ethylenecholestryl ether, and perfluoroalkyl suphonamide ethoxylate were able to form worm-like micelles with thermo-viscosifying behavior [32-35]. SP showed a transition state at a temperature range of 35-45 ºC, near its reported lower critical solution temperature (40 ºC). This behavior was also reported by Hughey *et al.*, [36] **Fig. 4**.

Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimeter (DSC): Fig. 5 shows the FTIR spectra of IBU, pure copolymer and IBU-PMs. The copolymer bands include a peak at 1662 cm^{-1} (C=O stretching), carbonyl amide bond at 1630-1695 cm^{-1} and an ester bond at 1755 cm^{-1}. The carboxylic acid of the IBU carbonyl stretching appears at 1724 cm^{-1} [37-39]. Regarding IBU-PMs, the comparatively low concentrations of IBU, coupled with the large molecular weight of the copolymer (90000-140000 g/mol), would mask the appearance of the characteristic IBU peaks, with the FTIR spectrum of the copolymer being the more prevalent [40]. However, the carbonyl amide's observed shift from 1662 cm^{-1} to 1631 cm^{-1} suggests the existence of a drug-polymer interaction.

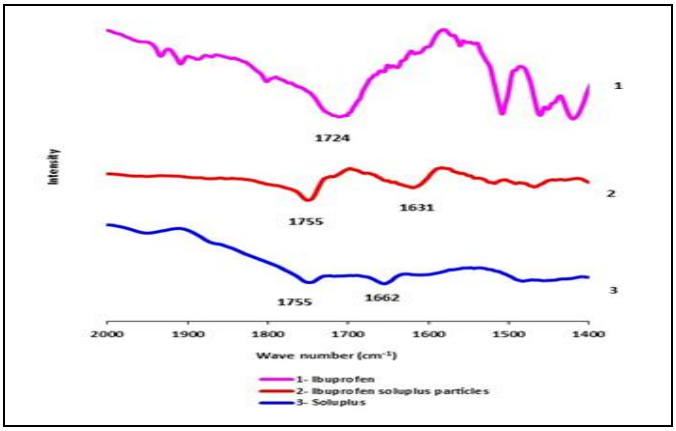

FIG. 5: FTIR SPECTRA OF IBUPROFEN, IBUPROFEN CO-POLYMER PRECIPITATED NANOMIECLLES AND CO-POLYMER

Fig. 6 shows the DSC thermograms of IBU, SP copolymer, and IBU-PMs. The sharp endothermic peak observed in the thermogram of IBU at 72 ºC represents the drug's endothermic melting [41]. The DSC thermogram of pure copolymer showed a broad endothermic event ranging from 50 ºC to 75 ºC, similar to the reported glass transition temperature (Tg) of the copolymer [38]. The shifting and broadening of the IBU melting point in the IBU-PMs suggest additional physical attractive bonds between the drug and the polymer [42].

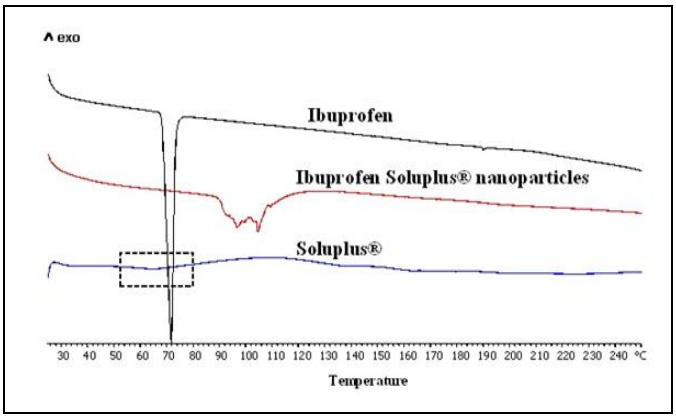

FIG. 6: DSC THERMOGRAMS OF IBUPROFEN, CO-POLYMER AND IBUPROFEN COPOLYMER NANO-MIECLLES

***Ex-vivo* Permeation Study: Fig. 7** shows the *ex-vivo* human skin permeation study results using the infinite dose technique. Such techniques avoid drug depletion from the donor compartment during the experiment and allow steady-state conditions. The diffusion parameters, including the cumulative amount of drug permeated at 28 h (Q28), the time to reach the steady-state (tlag), steady-state flux (Jss) and enhancement ratio (ER) were calculated and are presented in **Table 1**.

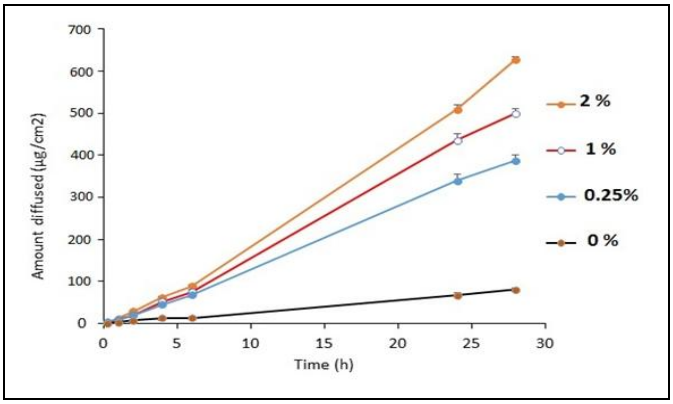

FIG. 7: *EX-VIVO* SKIN PERMEATION OF IBUPROFEN COPOLYMER NANOMICELLES PREPARED USING DIFFERENT CONCENTRATIONS OF THE CO-POLYMER

The ER is defined as the ratio between the mean flux of the IBU-PMs to the mean flux of the test drug solution (used as a control). It was seen that the 2% w/v copolymer micelles demonstrated significantly faster and higher skin permeation in comparison to the control after five h. No significant difference was found between the 1% w/v and 2% w/v copolymer micelle system.

Still, significant differences were observed between the concentrations mentioned above and the control, as well as the other concentrations. The IBU-PMs showed a significant improvement in permeation parameters (Jss, Q28h, ER) in comparison to the control.

TABLE 1: SUMMARY OF PERMEABILITY STUDY PARAMETERS OF THE CONTROL AND DIFFERENT IBUPROFEN-CO-POLYMER NANOPARTICLES (n=3)

Soluplus %	Q_{28h} (µg)	Flux, J_{ss} (µg $cm^{-2}h^{-1}$)	T_{lag} (h)	ER
0.25	385 ± 5.8	9.1 ± 25	1.7 ± 0.15	7
1	490.0 ± 7.8	11.9 ± 0.21	2.3 ± 0.22	9.2
2	650.6 ± 8.1	13.8 ± 0.22	2.4± 0.14	10.6
Water (control)	73.0 ± 1.0	1.3 ± 0.22	4.8 ± 0.2	-

CONCLUSION: IBU-PMs showed nanometric particle size and micellar solubilization caused a significant increase in the solubility of IBU. Additionally, the statistically significant increase in drug flux, cumulative amount permeated, and the enhancement ratio suggests the feasibility of using Soluplus to prepare nano-sized polymeric micelles as a drug delivery system of Ibuprofen.

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CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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