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IN-VITRO STUDIES OF PREDNISOLONE PRE-FORMULATIONS RELEASED FROM VARIOUS OINTMENT-BASES, FACTORS AFFECTING PENETRATION RATE AND PENETRATED AMOUNT

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ABSTRACT

In this pre-formulation study, the effect of individual factors influencing the penetration rate of drugs incorporated in various topical vehicles has been in-vitro investigated. The water poor soluble prednisolone is chosen as a model drug. To increase the dissolution behavior of prednisolone (P), co-precipitates of it with polyvinyl-pyrrolidone^{25}, (P/PVP^{25}-coprs), polyethylene glycol^{6000}, (P/PEG^{6000}-coprs) and adsorbents with Aerosil^{200} (P/A-^{200}-adsrob) were prepared and in-vitro tested. A significantly increased dissolution in purified water was obtained with the co-precipitate **F_1**, consisting of 10-wt% prednisolone and 90-wt% PEG^{6000}. As **F_1** was incorporated in various model-vehicles insignificant penetration profile was achieved. This effect was in fact due to the high concentration of PEG^{6000} in the vehicles, which has increased the bulk viscosity of the ointments, that resulted on the one hand in restricted drug particles movement between the phases and on the other between the external phase and the artificial membrane. In

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contrast, **F_2** consisted of 50-wt% Prednisolone and 50-wt.%/ PEG^{6000}-copr, showed a slight increase in drug solubility compared to the corresponding physical mixture as well to pure P. As **F_2** was incorporated in aqueous emulsifying wool wax-base, (WHES) a greater penetration rate into the synthetic membranes has resulted, and no change in the crystal form of P could be observed throughout the study time period of 70 hours. All other pre-formulations, (prefs) showed negligible increase in the solubility of P. X-ray diffractions studies of prednisolone-PVP^{25}-coprs and those of drug/$Aerosil^{200}$-adsorbent, indicated changes in the crystal form of P into monohydrate, which probably happened during the co-precipitation and adsorption of the drug and also during the incorporation of the pre-formulations into ointments. This change was specifically due to the very few amount of water present in ethanol 96 %v/v used as solvent for the preparation of the P-co-precipitates and adsorbents (= prefs) and also due to water available in the external phase of all used o/w-emulsions type ointment-bases.

KEYWORD:

PEG^{6000}, PVP^{25}, $Aerosil^{200}$, prednisolone, pre-formulations, ointment-bases, penetration rates, artificial membrane, polymorphism, X-ray diffractometry.

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INTRODUCTION

Prednisolone (P) has moderate anti-allergic and anti-inflammatory actions. This advantage is often used topically to treat various skin diseases[1]. Prednisolone is poor water-soluble, and it forms with water a sparingly water-soluble monohydrate (mhydr). Moreover, micronized prednisolone particles tend to agglomerate, resulting in reduction of the available surface area that might additionally affect negatively drug solubility in the outer aqueous phase of o/w-emulsions type topical vehicles, and hence lower its optimal release behavior from the vehicle[2, 3, 4]. Ointments are multi-phase disperse systems, having dermal actions that comprise a complex process by which not only the active substance, but also the vehicle as well as the skin itself could play a significant role[5]. In dermatology it is to differentiate between high and low permeable skin types[6]. Thus, the choice of a vehicle is usually determined by one of these two factors. When o/w-bases are used; water will evaporate, leaving behind a cooling and anti inflammatory effect that might make the desired corticosteroid therapy more efficient[7, 8]. Generally, for a substance to penetrate into the skin, a specific amount of it must initially dissolve in the vehicle. The dissolution rates of a substance in a base determine the extent and rate of penetration into the skin. Moreover, the penetration of a dissolved drug into the skin is often dependent on the drug's partition-, and diffusion-coefficient that exist between the external and internal phases[9]. An increase in the dissolution rate of prednisolone in the aqueous phase of a w/o-vehicle may enhance its penetration rate into the horny layer, which might probably results in therapy optimization and reduction in treatment-costs. Methods to improve the dissolution rate of a drug in the vehicle other than particle size reduction are many. One such a method is to dissolve the drug in an organic solvent, suspend in the drug solution hydrophilic non-toxic drug-carriers, or -adsorbent having a large surface area and a porous particle structure, and subsequently evaporate the solvent to complete dryness. On the surfaces of each obtained product, the drug may probably lie loose, and when it contacts water, an improved drug dissolution rates may results[10, 11]. To achieve this effect, prednisolone was dissolved in ethanol 96 %v/v, and in the resulting drug solution excess amounts of PEG^{6000}, PVP^{25} and A-200 were suspended respectively and subsequently the solvent was withdrawn from the preparations.

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The purpose of this study was to improve via technological means the in-vitro penetration rate of prednisolone into artificial membranes and to investigate factors that might have an influence on the penetration of the drug.

2. MATERIAL AND METHODS

2.1. MATEIALS

Micronized prednisolone, tetrazole blue, ethanol 96v/v%, methanol, (Merck KGaA, Darmstadt, Germany), hydrophilic fumed silica (Aerosil-$^{200®}$, A-200) (Degussa AG, Dűsseldorf, Germany), polyvinyl-pyrrolidone^{25} (Kollidon = PVP^{25}), polyethylene glycol^{6000}, (PEG^{6000}), (BASF AG, Ludwigshafen, Germany), dimeticone oil^{200}, dodecanol, collodion 4%v/v, chloroform, potassium hydroxide, (Laborchemie, Apolda, Germany). All substances used were of pharmaceutical grade.

2.2. METHODS:

2.2.1 Preparation of the pre-formulations, (pref.)

Prednisolone-co-precipitates, (P/copr.) and –adsorbents, (P/adsorb) were prepared by dissolving excess weights of prednisolone (P) in ratios of 1:9 and 1:1, (1.0 g and 5.0 g) in 250.ml ±2% ethanol 96 %v/v. Corresponding weights of PEG^{6000}, PVP^{25} and Aerosil^{200}, (each 9.0 g and 5.0 g) were suspended in the drug solutions and the resulted suspensions were then stored for 4 hours at 25ºC ±2º to facilitate P dissolution and sufficient swelling of the drug/carriers/adsorbents. The solvent was then withdrawn via a vacuum rotary evaporator at 70-80ºC and to ensure complete solvent-removal, all samples were placed over silica gel in vacuum desiccators for 72 hours and again in a vacuum oven by 25ºC ± 2º for 8 hours[11].

2.2.2. Saturation solubility of prednsolone- and –monohydrate in pure water

Excess weights of predinsolone (250.0 g) and monohydrate; (262.2g) were dissolved in 100.0 ml ±2% pure water. The solutions were gently shaken for 4 days at 25ºC ±2º. The resulted saturated solutions were centrifuged by 500rpm and subsequently filtered through a filter medium of 0.5µm diameter (G4, Sartorius, Germany). 2.0 ml ± 2% of the filtrates were withdrawn, and diluted with purified water to 100.0 ml ±2%, (n = 6). These concentrations were then detected in a UV spectrophotometer at λ_{max} = 248 nm

(UV 240, PC 286, Shimadzu scientific instruments Inc.). The measured saturation concentrations for prednisolone and its monohydrate were **97.1** μg/ml **27.4** μg/ml respectively.

2.2.3. Dissolution test for pure prednisolone & the prednisolone pre-formulations, (P/pref.)

Excess weights of prednisolone (25,0 mg), and the corresponding amounts of 10-wt% P/prefs; (2.5g P-wt10% co-precipitate/adsorbent, and 0.5 g of the 50-wt% P + 50-wt.% carriers) were placed in a paddle apparatus DT600 (Erweka, Germany), previously filled with 1.0 L ± 2% purified water, having a constant temperature of 37ºC ± 2% and a rotation speed of 50 rpm. The maximum dissolution test time period was 6 hours (hrs). At predetermined time points aliquots of 5.0 ml ±2% were withdrawn and each removed sample was replaced with an equal volume of pure water, and the samples were appropriately filtered via a 0.5μm filter-medium (Sartorius, Germany) and analyzed by UV at λ = 248 nm. Six tests were made and the results recorded as an average.

2.2.4. Saturation solubility of prednisolone in soft liquid paraffin and light fluid wax

Soft liquid paraffin and light fluid wax were constituents of some used vehicles; therefore it is important to determine prednisolone saturation solubility in both fluids. 255.0 mg P was dissolved respectively in 100.0 ml ± 2% soft liquid paraffin and light fluid wax[200]. The samples were then shaken for 4 days at room temperature to achieve saturation solubility. Afterwards the samples were centrifuged by 1400rpm for 25 minutes and subsequently passed through a 50μm filter medium under vacuum. The saturation solubility for both soft liquid paraffin and light fluid wax were 79.0μg/ml and 29.5μg/ml respectively.

2.2.5. Preparation of the synthetic membranes

The in-vitro penetration evaluation was preformed on artificial multi-layer membrane system described previously[12, 13]. A defined amount of each pref (10mg) was applied onto the acceptor system that was placed in a cell having a fixed application area of (4 cm^2). The acceptor-system consists of a mono-membrane, chosen to maintain sink environment. The experiments were carried out six-fold on a temperature controlled water bath at 32ºC±2. At a predetermined time points, the assembly was removed from the water bath, each membrane was rubbed from excess ointment, extracted with chloroform. 2.0ml±2% were withdrawn from each extract, mixed with 0.2ml±2% of a 0.5% tetrazole blue chloride solution and subsequently 0.3ml of a 0.03 molar methanolic potassium hydrochloride solution was added. The drug concentration was analyzed photometrically by λ = 525nm.

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2.2.6 Powder X-ray diffractometry

Wide angle X-ray scattering measurements were done on a Philips type Micron 1011, X-rays generator having a copper anode (Ni-filtered Cu Kα radiation, λ = 1.5418.10-1 nm, 40 kV/30mA, Philips industrial & Electro acoustic systems divisions, Almelo, Holland). The radiation scattered in the crystalline section of the samples was measured with a vertical diffraction control unit (URD 63 (Freiburger praezisionsmechanik GmbH, Freiburg, Germany). Patterns were obtained by using a step width of 0.02º with a detector resolution in 2θ between 4 and 40° at 25°C.

3. RESULTS AND DISCUSSION

3.1 Dissolution behavior of P, its -monohydrate. and the pre-formulations

The results of the dissolution patterns of pure P, and the P–prefs, **F1**, (10-wt%P + 90-wt% PEG^{6000}), **F2**, (50-wt% P + PEG^{6000}), **A1**; (10-wt% P + 90-wt Aerosil^{200} = A-200): **A2**, (50-wt P/A-200); **F3**, (10-wt% P/90-wt% PVP^{25}) and **F4**; (50-wt% P/PVP^{25}) and their quantitative composition are presented in Figure 1 and listed in table 1.

Figure 1, showed that P is poor water-soluble, and after 6 hours, only negligible increase in its solubility has occurred. In contrast, the dissolution of the copr **F1** was significantly enhanced compared to that of pure P. Moreover, the curve profile of **F1** indicated that in the first hour higher saturation solubility was obtained and it remained approximately constant for 6 hours. This effect was probably due to the high amount of PEG^{6000} (90-wt %) present in the pref. PEG^{6000} is water-soluble, with a relatively high surface area that might have enhanced the wettability of P, which may improve its solubility[10, 11].

The dissolution patterns of the prefs, **A1**, **A2, F3** and **F4** indicated insignificant increase in dissolution during the entire test time period. However, the copr **F2**, showed a slight enhancement in dissolution profiles compared to that of pure prednisolone.

To evaluate any changes in the crystal form of P that might have happened during the preparation of P/prefs, X-ray diffraction studies for pure P, its mhyd, the coprs, **F1**, **F2** and their corresponding physical mixtures were made and the results listed in table-2.

PVP^{25} is an amorphous material[14, 15]. Our X-ray diffraction patterns, (XRDP) of the physical mixture, consisted of 10-wt% P and 90-wt% PVP^{25} showed that the mixture was completely amorphous.

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Only two insignificant small peaks at 2θ = 15.4º and 17.4º were present. The XRDPs of **F_3** indicated the presence of small peaks similar to those of pure PVP[25], (no graph, presented). A comparison of the XRDPs of **F_4** with those of the corresponding physical mixture showed that P was partially changed into mhyd, happened during the co-precipitation of P with PVP[25]. Thus, the peaks at 2θ =14.25° and 15.55° were of the mhyd (2θ = 14.3° and 15.6°). The shoulders at 2θ = 13.8°, as well the peaks at 2θ =15.0°, 16.2° and 17.9º indicated that unchanged P was also available.

Aerosil[200] is an amorphous material with large surface area [17, 18]. The XRDPs of a physical mixture consisted of 10-wt% P and 90-wt%-Aerosil[200] showed very small peaks at 2θ = 15.5º and at 20.23º, but because of their shorter heights, their position could not be exactly determined. Presumably the peak at 15.5º was of P (pure P at 2θ = 15.1º) and not of the mhyd (2θ = 15.6º).

The XRDPs of the corresponding adsorbent **A_1** showed a single peak at 2θ = 15.5º, indicating the presence of a very few amount of P. This change has probably occurred during the adsorption of P on the surface of A-200, whereby some amount of P has changed into amorphous state, happened due to the few amount of water present in ethanol 96%v/v[16]. The XRDPs of **A_2** (no Figure shown.) showed very short peaks at 2θ = 13.8°, 14.25°, 15.1°, and at 15.4°, 15.8°, 16.2°, 17.6°. A comparison of these peaks with those of P and its mhyd showed slight deviation in their positions, suggesting that both crystal forms were present in the same mixture. When considering the heights of the peaks as a measure, it is possible to predict approximately the amount of P changed into mhyd. A comparison of the XRDPs of **F_4** with those of **A_2,** showed that the adsorption of P on the surface of Aerosil[200] has changed the crystal form of a few amount of P into its mhyd.

PEG[6000] is a crystalline polymer, water-soluble, has a helical structure, and hence is capable to transform drugs into hydrates[19], happens by entrapping small drug-molecules in his double helical structure, in the sense of a solid solution, that might result in enhanced solubility of drugs. The peaks presented in table 2 permits two statements:

First, no change in the crystal form of P has occurred, amorphous conditions were not present. Second, the position of the peaks deviates in some cases from those of pure P. The peaks were often rounded, because of the low concentration of P in the mixture, so that their exact positions could not easily be determined. Thus, the XRDPs confirm the conclusion that P laid mostly in the P/PEG[6000]-coprs as a pure drug. XRDPs of the physical mixture showed peaks at 2θ = 15.5° and 15.8°, which could not clearly be ordered either as of P or of pure PEG[6000]. In fact, the presence of mhyd in this mixture was unusual and

normally should not be available. Eventually, it is possible that due to the hygroscopic nature of PEG^{6000}, the mixture might have adsorbed atmospheric moisture, which transformed the crystal form of P into mhyd.

As shown previously, **F_1** indicated a significant increase in dissolution behavior compared to untreated drug and to the other prefs. This situation permits the conclusion that the enhanced dissolution profile of **F_1** could not be explained as a result of change in the crystal form of P rather due to the larger surface area of PEG^{6000}, its crystalline nature, high water-solubility and its higher surface-adsorption capacity, which resulted in enhanced P-wettabilty that has produced a higher dissolution profiles.

3.2 VEHICLES

The spectrum of the used ointment-bases comprises o/w- and w/o-emulsions type ointment-bases. **Table 3** shows the quantitative composition of the vehicles used for the in-vitro penetration into the artificial mono-membranes.

3.3. Evaluation of the results of the in-vitro penetration profiles of P/pre-formulations incorporated in various o/w- and w/o-emulsion type model-vehicles.

The extend of the in-vitro penetration into the synthetic membranes depended on the type of vehicles used and on the crystal form available in the base at the observation time period, was very different. WHES-SR is o/w-emulsion type ointment-base, meaning that only the amount of drug dissolved in the aqueous external phase can enter into the lipophilic membrane. A comparison of curve 1 (P) with curve 2 (mhyd) in Figure 2 confirms this statement. The amount of mhyd entered into the membranes was the lowest. As shown previously, P is more soluble in water (97.1 µg/ml) than the mhyd (27.4µg); also **F_1** indicated improved aqueous dissolution behavior. As **F_1** as well as all other 10-wt% P/prefs were incorporated in WHES, no increased penetration rates could be obtained. In contrast, as **A_2**, **F_2** and **F_4** were incorporated in WHES, a significant penetration profiles were achieved, compared to that of pure P. Thus, the different penetration rates of P released from the ointments (S-1 and S-2) explain on the one hand the importance of the drug solubility parameter in the outer water phase; and on the other hand, it is also important to consider that the drug-carriers/adsorbent might have changed negatively the physical parameters of the vehicle (e.g. viscosity, partition- and diffusion- co-efficients). PEG^{6000} and PVP^{25} are water- and lipoid-soluble; hence both carriers could change the properties of both the external and internal phases of w/o-vehicles.

$Aerosil^{200}$ is capable to build gels with water and hydrophobic materials, a property that could also change the physical parameters of both phases of o/w-emulsions. Accordingly, the amounts of $Aerosil^{200}$, PEG^{6000} and PVP^{25} in the 10-wt% P/prefs were higher than those available in the 50-wt% P/prefs, which

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indicate that different factors can affect the extent of drug release from the vehicles and hence its penetration rate into the mono-membrane, and these factors might overlap reversibly.

The incorporation of the prefs in Dimethicone^{200} 10-wt% ointment-SR has obtained similar results as those achieved with WHES.

WHES contains as a lipoid component, 10-wt% fluid wax. Dimethicone^{200} 10-wt% ointment-base was prepared from WHES, 10-wt% Dimethicone^{200} and 30-wt% water. As result to the addition of fluid wax^{200} the amount of lipoid in the DS-10-wt% ointment was slightly increased from 10% to 15%, and that of glycerol and the emulsifying wax were reduced, which made the vehicle slightly more hydrophobic. Thus, the following factors may be interrelated.

The differences in penetration profiles of P and mhydr were smaller than those obtained when WHES was used alone. A better penetration has again resulted, when 50-wt% P/PEG^{6000}-copr and P/A-adsorbent were incorporated in the DS10-wt%-vehicle. Generally, using DS-wt10% as a base showed no advantage over WHES. However, the high amount of lipid contained in DS-wt 10% could sooth eczema efficiently.

WWAS is w/o-emulsion type ointment-base, which consists of 50% WAS-ointment and 50%wt water. Therefore, it is impossible with WWAS to obtain an increased drug penetration from enhanced drug dissolution, because water lie in the internal phase. As **F_3** was incorporated in WWAS, (Figure 3, Curve S-22) the penetration rate of the drug has clearly decreased. A comparison of S-19 with S-17 showed an increased penetration rate of **F_2** into the membrane. This behavior explains that the higher penetration rate has not been obtained due to enhanced drug-water-solubility, rather due to other factors. Moreover, this comparison indicates also that the hydrophobic character of the observed model-vehicles is continuously in increase. Following this tendency it could be concluded that the penetration profiles of the P/prefs with improved dissolution behavior decreases with increased vehicle-lipophilicity. Moreover, the absolute amounts of prednisolone released from the vehicles and entered into the membrane has continuously decreased after 15 as well after 150 minutes, permitting the conclusion that w/o-emulsion type ointment-bases are more suitable for P as a base

To understand if any crystal changes has happened, during and after the incorporation of P in the various topical vehicles, X-ray diffraction studies were made, based on 10-wt% of P (1.0g pure P and 10.0g P/prefs/100g vehicle).

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The X-ray diffraction patterns of pure WHES indicated peaks at 2θ = 21.5° and 24.16°. Peaks at the range of 2θ = 12.0°- 17.0° counted as for P and mhyd were not registered. The XRDPs of a newly prepared S-45 (10% P in WHES) indicated a rapid crystal change of P into mhyd (Figure 6/a not shown). There were peaks registered at 2θ = 13.8°, 14.5°, 15.1°, 15.5°, and 16.2°. The peaks at 2θ = 14.5° and 15.5° confirm that the change in crystal form has occurred readily during the preparation of S-45, and their heights grow continuously during the observation time period (Fig 6-B, not shown). 38 hrs later there were only peaks present at 2θ = 14.4° and 14.9°, which indicates that the occurred crystal form change was most probably due to the relatively high amount of water available in the outer phase of WHES. Moreover, the positions of the peaks deviate slightly from those of pure P, suggesting that a complete change in the crystal form of P into mhyd has happened. Thus, from a biopharmaceutical viewpoint P-ointments based on WHES should be considered as mhyd-ointments.

The XDRPs of (10-wt% P/ DS-10-wt% ointment-SR) taken immediately after preparation indicated a fast change of the crystal form of P into its mhyd.

The XRDPs of pure WWAS showed that at the angle range of 2θ = 12º - 18º no peaks were present that might disturb the presence of P or its mhyd. The peaks immediately registered after the incorporation of P in WWAS and those taken after 120 hrs showed no significant change in its crystal form. WWAS is a lipophilic vehicle-type, by which an intimate contact between water and P is not possible. However, it is possible that the lipophilic phase (Vaseline) included in the vehicle has hydrophilized the crystal surface of P-particles. Accordingly, it could be concluded that the transformation of P into mhyd prepared with various vehicles has occurred in different velocities. This fact may affect greatly the bioavailability of P.

The evaluation of the X-ray-difractograms taken for ointments containing P/prefs was difficult to perform for many reasons. One time the crystal form of P has partially changed into mhyd readily during the preparation of the prefs, and on the other hand unchanged crystals of P were also available. Thus, the interpretation of these peaks should not be taken as reliable. The XRDPs of P/PEG^{6000}-copr/WHES taken immediately after preparation showed insignificant peaks, which might indicate a minimized P-crystallinity. After 90 minutes there were very weak peaks of P present and 70 hrs later no significant change in their positions or heights could be observed. Obviously P lies mostly in the vehicle as unchanged.

As this result was compared with those of S-45, it became evident that the incorporation of P-PEG^{6000}-copr in WHES has inhibited to a greater extent the transformation of P-crystal form into mhyd, this result suggests that the use of P/PEG^{6000}-copr in WHES has minimized the formation of mhyd. This

situation can be considered as an explanation for the improved drug penetration rates, released from vehicles containing 50-wt% P/prefs.

The X-ray studies of ointments containing P/PVP^{25}-copr, and/or P/A-200 incorporated in WHES could not be accurately evaluated, because the peaks were very small, which might indicate a reduced P-crystallinity and/or an amorphous state. This fact became clearly evident, as we have had compared; for example the XRDPs of S-45, (fig 6, curves-A, B, C, not shown here) with those of S-48 and S-49, (each contains 10% P as prefs, Figures not shown). XRDP of S-50 (10% P as 50-wt% PVP^{25}-copr/WHES) is another example for the same behavior. The peaks taken 95 hrs after preparation indicated that the incorporation of the 50% prefs in WHES has probably reduced the crystallinity of P and hence might have inhibited its total change into mhyd. As justification for this interpretation, the peaks at 2θ = 13·8º; 15·°; and 16·1° are similar to those of pure P. XRDPs of S-45 showed that at this time P lied in WHES only as mhyd. One can conclude that the penetration of the poorly water-soluble drug co-precipitated with PEG^{6000} prepared in ratio 1:1 and incorporated in WHES was significantly increased compared to the untreated drug.

ACKNOWLEDGEMENT

The author is very much grateful to Prof. G. Zessin of the department of pharmaceutics/ institute of pharmacy and Prof. R. Pollandt from the department of physical chemistry/ institute of chemistry/ Martin Luther University/Halle, of Germany for their valuable theoretical and technical support.

Table 1: Dissolution profiles of the prednisolone/pre-formulations, **F_1, F_2, A_1, A_2, F_3** and **F_4**, in pure water at 37°C, by rotation speed of 50 rpm, paddle DT600 USP, (n = 6 tests, ±SD = mean values)

	CONCENTRATIONS, [µg/ml]											
Time, (hrs)	prednisolone	F1	SD	F2	SD	F3	SD	F4	SD	A1	SD	A2	SD
1	14.6± 3.6	28.6± 1.8		20.6± 3.3		20.8± 0.8		19.4± 4.5		16.7± 3.0		18.7± 4.6	
2	17.8± 5.8	29.4± 9.0		21.4± 1.1		21.9± 3.5		20.7± 4.9		18.8± 6.3		19.6± 1.1	
3	19.3± 4.2	31.3± 9.8		23.1± 2.5		22.8± 3.4		21.6± 8.8		19.5± 8.7		20.4± 2.5	
4	19.6± 3.5	30.8± 12.4		24.0± 2.3		23.5± 2.6		21.5± 1.5		19.9± 7.3		21.4± 5.4	
5	19.8± 4.1	30.4± 3.80		23.5± 2.5		22.8± 7.6		20.3± 2.4		19.4± 9.9		19.4± 3.9	
6	20.4± 3.3	29.8± 11.5		23.1± 4.6		20.6± 3.4		20.0± 1.3		19.4± 9.9		19.4± 3.9	

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Table 2. X-ray diffraction patterns of pure prednisolone, its mono-hydrate, and the physical mixtures with PEG ^{6000}, (**F_1** and **F_2**)

Preparations	Peaks at 2θ						
Pure Prednisolone (**P**)	13.8º,	15.1º,	16.2º,	17.9º			
Pure Prednisolone-monohyd.	14.3º,	15.6º					
Pure PEG ^{6000}	13.0º,	13.5º,	14.5º,	15.05º			
Physical mixture of 10-wt% P							
+ 90-wt PEG ^{6000}	13.5º,	13.9º,	14.6º,	15.1º,	15.5º,	16.2º,	17.65º
Co-precipitate **F_1**	13.7º,	15.04º,	15.5º,	15.9º,	16.3º,	16.8º	
Physical mixture of 50-wt% P							
+ 50-wt% PEG ^{6000}-	13.7º,	14.9º,	15.3º,	15.8º,	16.0º,	17.9º	
Co-precipitate **F_2**	13.8º,	15.1º,	15.6º,	16.3º,	17.9º		

Table 3. Qualitative composition of the ointment-bases used

1. Aqueous emulsifying wool-wax ointment-SR/GER, (WHES)	
Emulsifying wool-wax	21.0g
Light Silicone oil ^{200}	10.0g
Glycerol	5.0g
Propyl-paraben	0.06g
Methyl-paraben	0.14g
Ethanol 96%v/v	1.80g
Purified water ad	100.00g
2. Wool wax alcohol ointment-base-SR, (WAS)	
Wool wax-alcohols	6.0g
Cetostearyl alcohol	0.5g
White Vaseline	93.5g
3. Aqueous wool wax alcohol ointment-base-SR, (WWAS)	
Wool wax-alcohols ointment-base (**WAS**)	50.0g
Purified water	50.0g
4. Dimethicone oil^{200} ointment-base 10wt%-SR (DS10%wt)	
Dimethicone oil^{200}	10.0g
Aqueous emulsifying wool wax ointment-base (**WHES**)	60.0g
Bacteriostatic water	30.0g

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Table 4. In-vitro penetration rates of the pre-formulations, **F_1, F_2, A_1, A_2, F_3**, and **F_4**, incorporated in aqueous emulsifying wool wax ointment-base-SR/Ger. (= **WHES**)

Oint. Nr.	Time Min	Penetr. Amount (%)SD	AUC (%)	Oint. Nr.	Time (Min)	Penetr. Amount (%) SD	AUC (%)	Oint. Nr.	Time (Min)	Penetr. Amount (%) SD	AUC (%)
S-1 (0.25% P + WHES	15 45 60 90 150	32.9±8.50 41.3±18.5 43.7±19.0 46.1±7.80 48.0±12.3	934.8	S-2 (0.25% mhyd + WHES	15 45 60 90 150	30.6±14.5 32.2±11.5 35.8±11.6 35.8±11.6 39.8±5.69	792.8	S-3 (F1+ WHES)	15 45 60 90 150	34.6±3.17 36.0±4.50 37.7±2.55 42.4±2.22 44.5±1.95	874.0
S-4 (F2 + WHES	15 45 60 90 150	45.0±2.34 54.8±4.13 57.4±1.72 59.4±19.2 63.4±3.03	1187.2	S-5 (A1 + WHES)	15 45 60 90 150	34.9±6.26 40.0±6.08 43.5±2.54 48.1±2.38 51.6±3.05	961.0	S-6 (A2 + WHES)	15 45 60 90 150	55.4±2.90 59.0±2.53 61.1±3.22 62.8±2.07 66.3±7.44	1260.2
S-7 (F3 + WHES	15 45 60 90 150	34.1±2.75 38.8±3.14 41.1±2.09 43.5±2.77 47.0±3.23	905.6	S-8 (F4 + WHES	15 45 60 90 150	50.4±3.55 56.1±1.77 60.8±3.35 63.0±2.39 68.4±3.23	1246				

Abbreviations: oint. = ointment. Nr. = Number. S = reference to ointment. Penetr. = penetrated. AUC = area under the curve. SR = standard formulae. Ger = Germany. SD = standard deviation mean values.

Table 5. In-vitro penetration rates of the prednisolone-pre-formulations, **F_1, F_2, A_1, A_2, F_3** and **F_4**, incorporated in aqueous wool wax alcohol-ointment-base-SR/Ger. (= WWAS)

Oint. Nr	Time (Min)	Penetr. Amount (%) SD	AUC (%)	Oint. Nr	Time (Min)	Penetr. Amount % SD	AUC (%)	Ointment Nr	Time (Min)	Penetr. Amount (%) SD	AUC (%)

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S-17 (0.25% P + WWAS)	15	38.1±2.20		S-18 (0.25% mhyd + WWAS)	15	40.5±1.49		S-19 (F1 + WWAS)	15	48.9±2.07	
	45	39.5±2.53			45	42.0±1.70			45	52.9±1.60	
	60	41.9±1.58			60	44.0±1.23			60	55.2±0.74	
	90	45.1±2.05			90	46.6±2.50			90	57.7±1.09	
	150	47.2±1.82	931.9		150	50.0±1.26	967.0		150	61.6±2.09	1163.4
	15	40.0±1.80		S-21 (A1 + WWAS)	15	51.0±0.70		S-22 (A2 + WWAS)	15	33.2±1.99	
	45	41.3±1.55			45	52.3±2.10			45	35.7±1.80	
S-20 (F2 + WWAS)	60	42.0±1.28			60	55.0±0.90			60	36.0±2.36	
	90	44.1±1.94			90	57.0±1.10			90	39.0±1.64	
	150	46.1±1.85	930.0		150	60.3±1.64	1156.2		150	41.4±1.00	832.8
	15	49.0±1.07									
	45	50.0±1.64									
	60	52.5±1.52									
S-23 (F4 + WWAS)	90	54.0±1.77									
	150	57.1±1.94	1110								

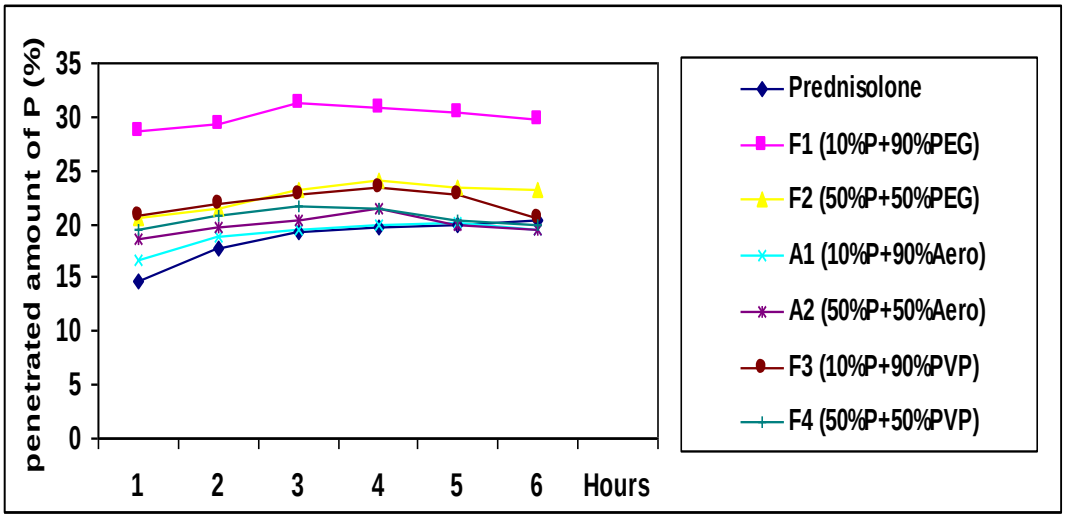

Figure 1: Dissolution profiles of the prednisolone/ pre-formulations, **F_1, F_2, A_1, A_2, F_3** and **F_4** in pure water at 37°C, by rotation speed of 50 rpm paddle DT600 USP, (6 = tests, ±SD = mean values).

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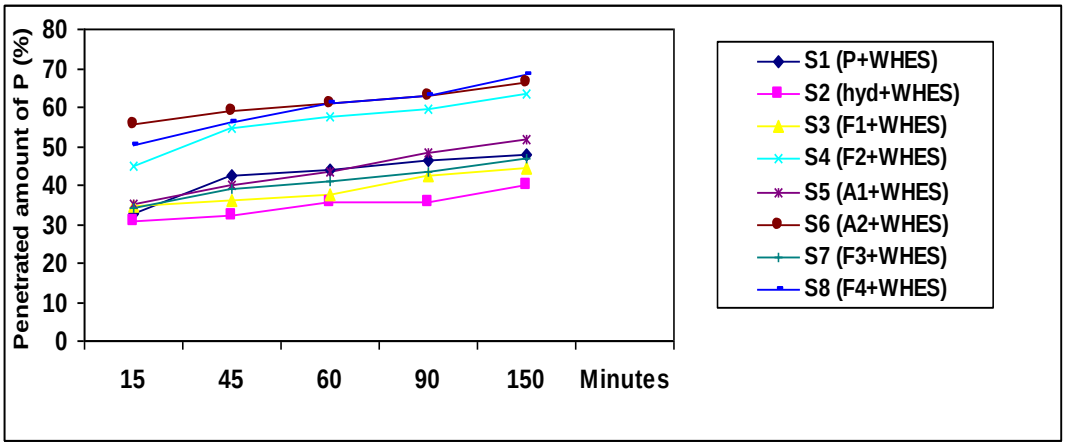

Figure 2: In-vitro penetration rates of the prednisolone/ pre-formulations, **F_1, F_2, A_1, A_2, F_3** and **F_4**, released from aqueous emulsifying wool wax ointment-base-SR/Ger, (WHES).

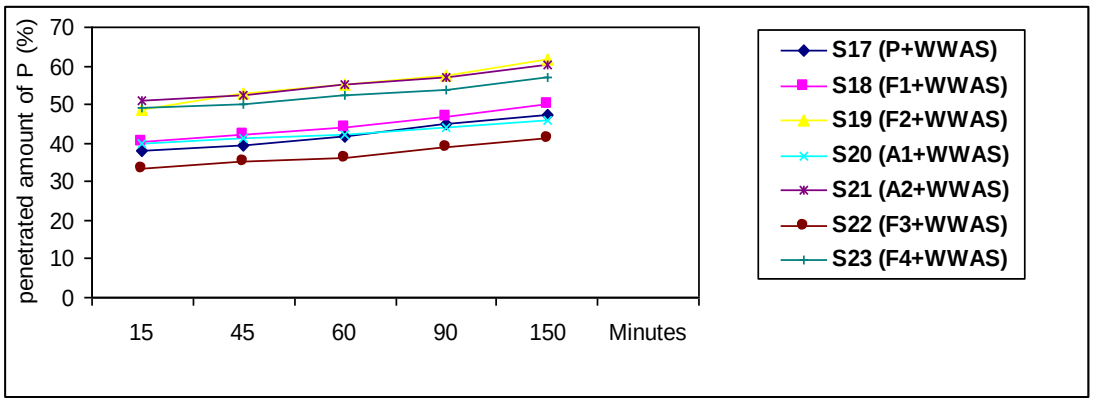

Figure 3: In-vitro penetration rates of the prednisolone/ pre-formulations, **F_1, F_2, A_1, A_2, F_3** and **F_4**, released from aqueous wool wax alcohols ointment-base/SR-Ger, (WWAS).

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