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RELEASE OF SALICYLIC ACID FROM NEW MULTIPHASE BASES WITH CONSIDERATION OF THE PREPARATION METHOD

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Abstract: The study evaluated the release of salicylic acid with new two multiphase ointment bases: Fitalite™ and Nourivan™ Antiox. Fitalite™ is a cream-gel base while Nourivan™ Antiox is a cream oil in water. Salicylic acid is a substance often used in the formulation of semi-solid dosage forms applied on the skin. The release rate of salicylic acid was examined depending on the base and the particle size of the active ingredient. For this purpose, formulations containing 5% salicylic acid were prepared and used for the study. Three different methods were used for the incorporation of salicylic acid into the bases: non-grinded, ground with the base for 15 minutes, and concentrate of salicylic acid with white soft paraffin (1 : 1). Measurements of the particles of the active substance in each of the preparations were also taken. Salicylic acid has been shown to be released to a greater extent from Fitalite ™ base. Qualitative analysis of the composition of the bases, in studies conducted by the Department staff, allows concluding that the amount and release rate of salicylic acid from the bases is influenced by its viscosity. This parameter has a significant impact on the level of trituration of salicylic acid. It was also found that the concentrate of salicylic acid with white soft paraffin (1 : 1) reduces the time of preparation of a suspension-type ointment with salicylic acid, wherein the particle size accomplishes the requirements of pharmacopeia.

Keywords: salicylic acid, semisolid dosage forms, in vitro release, particle size, Fitalite™, Nourivan™ Antiox

Knowing the critical parameters influencing the quality of the drug allows the exclusion of operations leading to the deterioration of the quality of the prepared formulations (1). In dermatological therapy, semi-solid forms of the drug, such as ointments, creams, or gels, are most often used to achieve epidermal, endodermal, diadermal, or transdermal effects (1). The applied bases are assessed in terms of spreadability, water binding capacity, active substance release, and ability to penetrate the skin (2). The effectiveness of the drug form applied to the skin depends on the ability to release the drug active substance from the base used. Therefore, it is important for therapeutic as well as qualitative purposes to know the parameters concerning, among others, the amount of active substance released *in vitro* (3, 4). This process depends on a number of factors related to the properties of the tested preparation. The physicochemical nature of the base and the drug substance itself are also important.

The study used salicylic acid, often applied in dermatology, among others in the form of ointments, pastes, oil, and ethanol solutions. The mechanism of action of salicylic acid is based on the dissolution of intercellular cement, which results in loosening the adhesion of corneocytes. This leads to the removal of the stratum corneum, starting from the outermost layer and progressing downwards (5, 6). Preparations with salicylic acid content between 1% and 10% have antiseptic effects, above this content, besides moisturizing, these products have keratolytic effects. This raw material in prescription formulations may exhibit bacteriostatic, fungicidal, anti-dandruff, antiperspirant, and photoprotective effects (6-8).

Salicylic acid can be used in combination with other topical therapies to treat psoriasis (9). Vender et al. observed that the skin condition of people with dry and/or scaly skin is significantly improved by the twice-daily application of a cleanser and a ceramide cream, which also contains salicylic acid

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(10). A pilot study by Danielson and Walter (2005) confirmed the effectiveness of using a 2% salicylic acid cream (Avosil) with a layer of hydrogel dressing (Avogel) in the treatment of hypertrophic scars (11).

The multicentre, randomized study showed that 0.5% 5-fluorouracil in combination with 10% salicylic acid solution is effective in the treatment of lesions in patients with mild to moderate hyperkeratotic (12). Jo et al. (13) described that a combination of low-dose oral acitretin (10mg/day), topical salicylic acid, and steroids could be effective in the treatment of Punctate Palmoplantar keratodermas (PPPK). Another study observed that 2% salicylic acid cream has similar efficacy with 0.01% adapalene plus 5% benzoyl peroxide in mild to moderate acne treatment (14). The efficacy and safety of salicylic in clinical trials in the therapy of psoriasis have been widely discussed in the review paper by Jacobi et al. (15).

The side effects of externally applied salicylic acid include irritation, excessive drying of the skin, and occurrence of contact allergy (16). Salicylic acid poisoning due to the absorption of a toxic dose through the skin has also been described. This applies in particular to newborns, infants, and young or elderly people with concomitant diseases, especially renal failure (17, 18).

Salicylic acid ointments are preparations in which the active substance is suspended in a base (suspension ointments). The particle size of the active substance above 90 μm may cause skin irritation during application. In the case of preparing semi-solid forms of the drug with the use of substances insoluble in the base, two methods of distributing them in the base are used: introducing a solvent for the drug into the base and emulsifying it into the base or dispersing it in the base. It is not recommended to conduct micronization of salicylic acid with the use of a volatile solvent such as ethanol. Even though ethanol influences the plasticity of the base by reducing its viscosity, which was confirmed in some papers (19-21), its application may be the cause of the recrystallization of salicylic acid and the appearance of the so-called "giant crystals".

For pharmaceutical compounding, in addition to the solid form of salicylic acid, there is also an ointment concentrate, prepared in equal parts with white soft paraffin (1 : 1). This product is an alternative to the highly irritating solid substance. Its use ensures safety for the person preparing the ointment, and also reduces the time of drug preparation, because the labor-intensive step of grinding the salicylic acid is omitted.

The aim of the study was to assess the kinetics of salicylic acid release *in vitro*, depending on the type of multiphase medium used, as well as on the method of preparation of the tested ointment formulation, including the method of salicylic acid grinding.

MATERIALS

Nourivan™ Antiox (Fagron, UK) – emulsion base oil-in-water (o/w) (ingredients: purified water, cetearyl alcohol, polysorbate 60, C13-C16 isoparaffin, C12-C14 isoparaffin, C13-C15 alkane, glyceryl stearate, PEG-75 stearate, polyacrylate 13, polyisobutate, polysorbate 20, polyurethane-39, stearyl behenate, cetyl alcohol, ascorbic acid, benzoic acid, sodium bisulfite, sorbic acid, tocopheryl acetate); Fitalite™ (Fagron, UK) – hydrophilic gel-cream base (ingredients: purified water, safflower oleosomes, polyacrylate 13, polyisobutene, polysorbate 20, benzoic acid, sodium carbomer, sorbic acid, tocopheryl acetate); Salicylic acid concentrate with white soft paraffin 1 : 1 (Fagron, Pharma Cosmetic, Poland); paraffin, white soft (Vaselinum album) (Fagron, Pharma Cosmetic, Poland); potassium dihydrogen phosphate, disodium hydrogen phosphate (Chempur, Poland). All materials used in the study were of the analytical grade and satisfy the requirements of standards and certificates.

METHODS

Preparation of ointment with salicylic acid

The ointment formulations with salicylic acid (5% w/w) were prepared on two multi-phase ointment bases: Fitalite™ (F) and Nourivan™ Antiox (N), with the use of the Unguator E/S (Gako, GMBH) recipe mixer. Salicylic acid was introduced into the bases in three different combinations: unground powder, ground with an equivalent amount of the bases applied for 15 minutes, and concentrate of salicylic acid with white soft paraffin in a 1:1 ratio. The ointments were mixed for 4 minutes at level 5 (1630 rpm). The composition of the ointment formulations is presented in Table 1.

Measurement of the particle size

The particle size of the salicylic acid was measured with an MT4300H microscope, Meiji Techno Co., Japan equipped with a software camera (Motic Image Plus 2). In the microscope slides, the size of 100 particles in the preparation was assessed at 100 times magnification. The particles were

Table 1. Composition of the formulations with salicylic acid.

Formulations	Vehicle (g)		Salicylic acid (g)	
N + SA	Nourivan™ Antiox	95	Salicylic acid – powder	5
N + rSA	Nourivan™ Antiox	95	Salicylic acid – powder, ground in a mortar	5
N + conc	Nourivan™ Antiox	90	Concentrate of salicylic acid with white soft paraffin in a 1 : 1 ratio	10
F + SA	Fitalite™	95	Salicylic acid – powder	5
F + rSA	Fitalite™	95	Salicylic acid – powder, ground in a mortar	5
F + conc	Fitalite™	90	Concentrate of salicylic acid with white soft paraffin in a 1 : 1 ratio	10

grouped into the following size ranges: below 30 μm, 30-60 μm, 60-90 μm, and above 90 μm. The percentage of each particle size range was then calculated.

Salicylic acid release assessment from the ointments

In the study, a pharmacopeia method for release from transdermal systems was used, using a paddle apparatus (EWEKA DT-600, Germany) with an extraction chamber (1). Accurately weighed (3.0 g) of the prepared salicylic acid formulations were placed in the extraction chamber and covered with a semipermeable membrane (Spectra/Por®2 Dialysis cellulose. MWCO: Fisher Scientific, Loughborough, UK) soaked in acceptor liquid. The extraction chamber was placed in 500 mL of pH 7.4 phosphate buffer, thermostated at 32°C, with a paddle speed of 50 rpm. Samples (3 mL) were taken, for 6 hours every half hour, for spectrophotometric determination with further dilution, and the volume was replaced immediately with fresh phosphate buffer solution to maintain the sink. The samples were analyzed for absorbance at a wavelength of 296 nm using the Cecil CE 3021 UV-Vis spectrophotometer (Cecil Instruments), and the concentration of salicylic acid was calculated from the standard curve: $y = 0.026x + 0.0332$; $R^2 = 0$. Each formulation was tested in triplicate.

The dissolution profiles of the different formulations of salicylic acid were compared using one-way ANOVA, using 12 Statistica (StatSoft, Inc.). $P < 0.05$ was considered statistically significant. A model-independent mathematical approach was also used to compare the dissolution profiles of the samples and the reference product using the difference factor (f1) and similarity factor (f2) (22).

Kinetics calculations

The release results were fitted with different kinetics models: zero order (μg salicylic acid release vs. time), first order (log of μg salicylic acid remaining vs. time), and Higuchi's model (μg salicylic acid release vs. square root of time). For each model R^2 values were calculated.

RESULTS AND DISCUSSION

The safety of the medicines used by patients depends significantly on the dose or concentration used. Professional literature has repeatedly emphasized the need to provide compounded medications, using the expertise of pharmacists to fulfill the medical needs of individual patients. This is particularly important in topical dermatological preparations for various skin diseases.

Therapy with the use of salicylic acid in semisolid forms of the drug requires the selection of a base adequate to the expected effects, which is related to the amount of released salicylic acid.

In this paper, new solutions were sought for the use of new ointment bases, taking into account their qualitative composition. Fitalite™ base can be used alone and is recommended especially for oily and seborrheic skin conditions (23). It can be used in the treatment and care of acne-prone skin and hyperpigmentation. On the other hand, Nourivan™ Antiox base, due to the presence of many emollients, such as cetyl and cetearyl alcohol, glyceryl stearate, isohexadecane, or isododecane, has strong moisturizing properties (24). It is therefore primarily intended for dry and very dry skin. Previous studies assessed the physicochemical properties of the Nourivan ™Antiox® base after adding selected solvents (water, 96% ethanol, castor oil, and glycerol in a ratio of 1 : 0.5 with castor oil and Peru balsam) and the stability of the base solvent combination based on rheological research studies (25). In rheological studies of the base, after 4 months of storage, the lowest rheological stability was demonstrated for the combination with Peru balsam. Another study showed that the formulation with Nourivan™ containing 5% hydroquinone was characterized by the best physicochemical stability, the highest permeability through both types of membranes (a synthetic membrane and

Table 2. Size of salicylic acid particles in formulations prepared using Nourivan™ Antiox or Fitalite™.

Particle size (μm)	% of individual particles in the ointment depending on the method					
	N + SA	N + rSA	N + conc	F + SA	F + rSA	F + conc
< 30	42.4	40.4	52.2	16.7	39.7	68.2
30–60	35.5	42.8	43.3	32.9	41.2	29.7
60–90	15.3	11.2	4.5	22.5	11.2	2.1
> 90	6.8	3.6	-/-	27.9	7.9	-/-

mouse skin), and the lowest cytotoxicity compared to formulations with Beeler's base used by Spanish pharmacists (26). The results of the study by Nguyen et al. have indicated that Nourivan™ is a promising vehicle for erlotinib, a substance used in the treatment of Olmsted syndrome (a rare congenital disorder characterized by bilateral mutilating palmoplantar keratoderma (PPK) and periorificial keratotic plaques with pruritic lesions) (27).

The size of the particles suspended in the base ointment plays an important role in sensory feelings. The presence of granularity does not give full comfort in the application of a semi-solid form of the drug. Table 2 shows the results of the measurement of the particle size of salicylic acid in the formulations made on the ointment base Nourivan™ Antiox® and Fitalite™® depending on the method of introducing the active substance (SA).

In the study, satisfactory results of salicylic acid grinding using two bases of different plasticity were obtained by using ready salicylic acid concentrate prepared with white soft paraffin. The use of prepared intermediates significantly accelerates the preparation of the drug, while maintaining pharmacopeia requirements. It was found that only when using a salicylic acid concentrate with white soft paraffin 1 : 1, the particle size in the prepared formulation did not exceed 90 μm (Table 2). Similar results with the use of white petroleum jelly or Hascobase as a base were obtained in the study by Czajkowska-Kośnik et al. (7).

A significant difference in the content of particles larger than 90 μm was also observed depending on the base. When using Fitalite™ base and previously unground salicylic acid, the content was approximately four times higher compared to Nourivan™ Antiox base. When the active substance was ground with Fitalite™ base for 15 minutes, approximately twice as many particles exceeding 90 μm were observed as for Nourivan™ Antiox base (Figure 1).

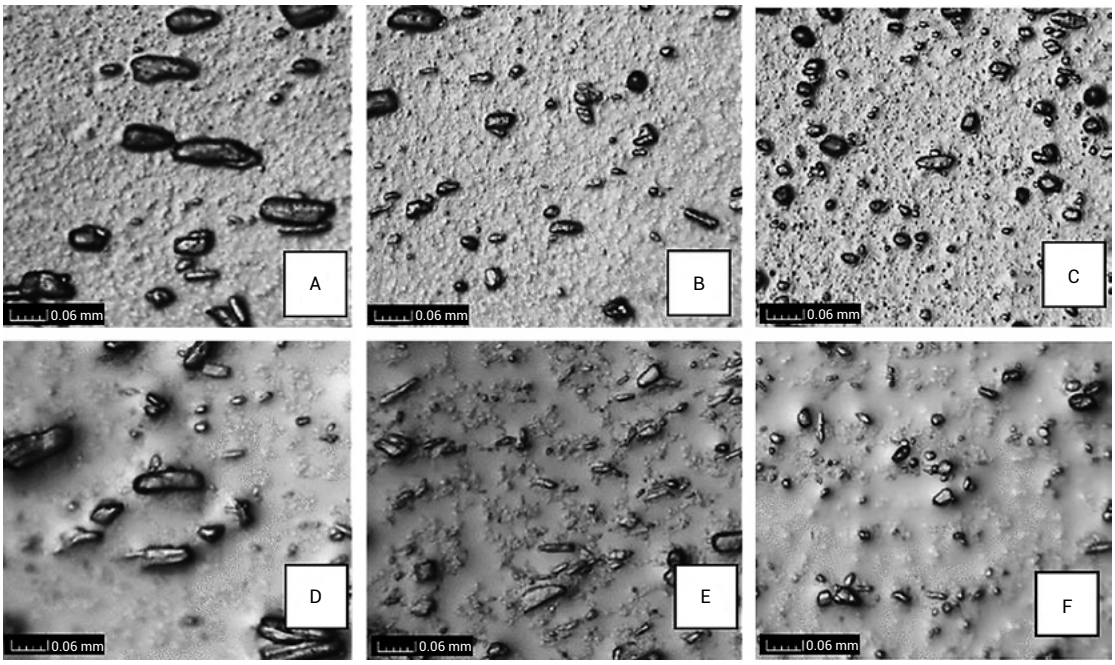

Figure 1. Microscopic image of salicylic acid particles in ointment bases (100x magnification). (A) N + SA; (B) N + rSA; (C) N + conc; (D) F+SA; (E) F + rSA; (F) F + conc.

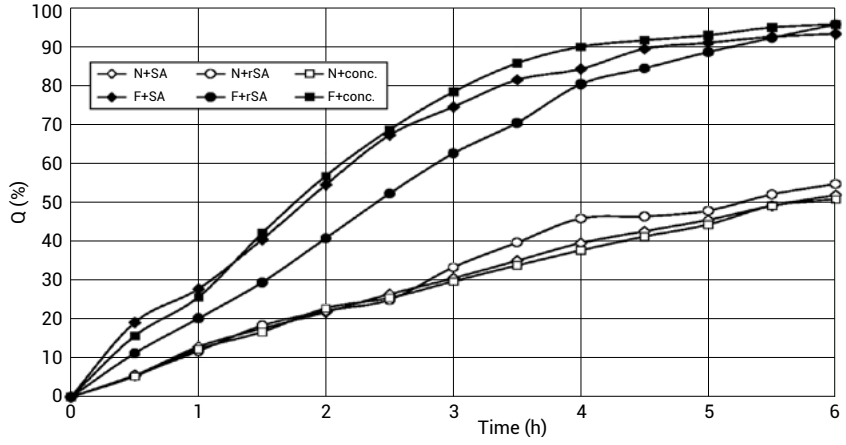

Figure 2. *In vitro* release profiles of salicylic acid from ointment bases.

The above differences may be related to the plasticity and viscosity of these bases. The lower plasticity of the Fitalite™ results in poorer dispersion of salicylic acid.

In the study of Winnicka et al. (28), it was reported that the grinding time, after which no particles larger than 90 μm were observed in the preparation, was 27 min. However, it should be noted that in the discussed study, the salicylic acid ointment was prepared on yellow petroleum jelly, with the previous levigation with liquid paraffin.

The amount of active ingredient released from semi-solid dosage forms may be indicative of the efficacy of a particular formulation. Figure 2 shows the dissolution profiles of salicylic acid ointments. In *in vitro* dissolution studies, it was observed that the amount of salicylic acid released from the Fitalite™ base was significantly higher (approximately 1.8 times, $p < 0.05$) compared to Nourivan™ Antiox. The resulting release profiles were compared using difference (f1) and similarity (f2) factors. The reference formulations are similar to the formulations tested in terms of the percent release as shown in Figure 2 also with the similarity coefficient (f2) for formulations based on Nourivan™ Antiox: 74.77 (N + rSA) and 91.91 (N + conc), respectively, while for formulations based on Fitalite™: 52.08 (F + rSA) and 74.55 (F + conc), in turn, the difference (f1) was: 7.52 (N + rSA), 2.99 (N + conc) and 11.96 (F + rSA), 4.07 (F + conc) as presented in Table 3. The relative difference between two curves f_1 values up to 15% indicates little difference between two dissolution curves, while drug products are considered similar when the calculated f_2 is between 50 to 100 (22).

Table 3. Difference factor (f_1) and Similarity factor (f_2) in terms of percentage release in the range of 0-6 h.

Formulation reference	Tested formulations	
N + SA	N + rSA	N + conc
Factor f_1	7.52	2.99
Factor f_2	74.77	91.91
F + SA	F + rSA	F + conc
Factor f_1	11.96	4.07
Factor f_2	52.08	74.55

Table 4. Kinetics release models used to describe the release of salicylic acid from various formulations.

Formulation	Cumulative release salicylic acid [%]	Kinetics release models			k_H [μg/cm² h$^{1/2}$]
		Zero Order R^2	First Order R^2	Higuchi R^2	
N + SA	52.03 ± 0.48	0.9893	0.8419	0.9959	1630.6
N + rSA	54.86 ± 1.34[b]	0.9716	0.8427	0.9833	1709.5 [b]
N + conc	50.94±0.31[b]	0.990	0.8409	0.9947	1573.4 [b]
F + SA	93.54 ± 0.17[a]	0.8743	0.751	0.9486	3754.2 [a]
F + rSA	95.97 ± 0.05[a, c]	0.8986	0.7939	0.9618	3977.9 [a, c]
F + conc	96.01 ± 0.67[a, c]	0.9673	0.8470	0.9883	3993.3 [a, c]

k_H - average release rate, R^{2-} Regression Coefficient, NS- not statistically significant. Statistically significant: [a]$p < 0.05$ compared to preparations prepared on Nourivan™ Antiox®, [b]NS compared to N + SA, [c]NS compared to F + SA.

In order to determine the kinetics of the release process, the amount of released salicylic acid per unit of diffusion area Qp (μg/cm^2) was calculated. The kinetic model was then fitted (Table 4). It was shown that the release occurs according to the Higuchi model.

The release rate constants (k_H) of salicylic acid from formulations F + SA and N + SA were: 3977.9 μg/cm^2 h$^{1/2}$ and 1630.6 μg/cm^2 h$^{1/2}$, respectively. For Nourivan™ Antiox base, the release rate of salicylic acid decreases in the order: N + rSA > N + SA > N + conc. However, in the case of the Fitalite™ base, this order is reversed, which means that the fastest release occurs from F + conc and the slowest from F + SA (Table 3).

These results indicate that salicylic acid releases better from the gel base than from the oil-in-water cream, which may be due to the lower viscosity of the Fitalite™ base compared to Nourivan™ Antiox. The multiphase medium used in the study – Fitalite™ is a cream-gel base, while - Nourivan™ Antiox, is an o/w cream. The differences in the viscosity of both bases result from their different composition. The higher viscosity of Nourivan™ Antiox is due to the presence of cetyl and cetearyl alcohol, glycerol stearate, and polyurethane – 39, which are absent in Fitalite™. These substances are responsible for the consistency of the preparations. In addition, Fitalite™ contains safflower oleosomes, which may promote the release of hydrophobic drug substances.

In a study by Thakker and Chern (29), it was shown that the amount of released retinoic acid is inversely proportional to the content of viscosity-increasing substances. A similar relationship was demonstrated for aceclofenac in the study by Dua et al. (19). Also in the study by Banyś et al. (20), where the release of diclofenac sodium from different ointment bases was studied, it was found that the highest amount of the substance was released from the glycerol-based gel base.

Studies have shown that salicylic acid is best released from hydrophilic bases, especially those containing propylene glycol (30). Semi-solid preparations, in which salicylic acid is encapsulated in lipid nanoparticles, are characterized by an initial faster release, which is associated with diffusion through the membrane of free molecules of the substance present in the aqueous phase. This solution applied by the manufacturer makes it possible to achieve a prolonged action of the drug. This, in turn, helps minimize the side effect of skin irritation and enhances the patient's positive sensory experience. Then the release slows down, which is related to the retention of salicylic acid in the nanoparticles (31).

Obtaining a satisfactory result in synthetic membrane dissolution studies does not necessarily indicate high skin permeation. This is due to the fact that hydrophobic substances have a high affinity for the lipophilic stratum corneum layer and can be retained in it. Moreover, the skin is an active barrier, unlike a neutral synthetic membrane.

CONCLUSION

The study showed that salicylic acid was released better from the gel substrate than from the oil-in-water cream-like substrate. A significantly higher amount of active ingredient was released into the acceptor fluid from the Fitalite™ base than Nourivan™ Antiox. The release rate constant (k_h) values were – 3754.2 μg/cm^2 h$^{1/2}$ for Fitalite™ compared to the calculated value for Nourivan™ Antiox of 1709.5 μg/cm^2 h$^{1/2}$. It was observed that the viscosity of the base influences the degree of grinding of active substance particles and significantly influences their release. Application of a ready concentrate of salicylic acid with white soft paraffin in a 1 : 1 ratio shortens the time of preparation of ointments of the suspension type and enables the preparation of ointments in which the size of the ground particles is compliant with pharmacopeia requirements. These results indicate that formulations made with Fitalite™, especially F + conc., need to be further investigated as new topical agents for the therapy of skin diseases.

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Conflicts of interest

The authors declare no conflict of interest.

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