Dermatol Ther (Heidelb) (2023) 13:391–398
https://doi.org/10.1007/s13555-022-00873-0

REVIEW

Supersaturation as a Galenic Concept for Improving the Cutaneous Bioavailability of Drugs in Topical Therapy

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Received: October 27, 2022 / Accepted: December 5, 2022 / Published online: December 21, 2022

ABSTRACT

The essential force that allows an epicutaneously applied drug to penetrate the skin is mediated by diffusion. The physicochemical properties of the skin tissue at the site of application and the concentration gradient of the dissolved drug between the vehicle and the stratum corneum are decisive here. One way to specifically improve these diffusion conditions is to use supersaturation. This uses the physical principle of the difference between the solubility curve and precipitation curve (Ostwald-Miers range). During the conversion of the application vehicle into the segregation vehicle, supersaturation of the dissolved drug substance in a solvent is achieved by evaporation, e.g., of a solubilizer. In principle, the change in solubility can also be achieved by heating and then cooling a solution. This principle has already been realized in a formulation of a fixed combination of calcipotriol and betamethasone dipropionate, two lipophilic drugs susceptible to hydrolysis, and is available on the market as a spray foam.

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Keywords: Galenics; Supersaturation; Cutaneous bioavailability

Key Summary Points

The cutaneous bioavailability of a topically applied drug depends on the galenic concept of the formulation

In addition to the physicochemical properties of the drug, its penetration is mainly dependent on its concentration gradient (Fick's diffusion law)

Immediately after application of the topical preparation, its vehicle undergoes metamorphosis, which causes molecular rearrangement of the vehicle components

To achieve the highest possible concentration gradient of a drug after application, the concept of supersaturation can be applied

In supersaturation, a stable solution is achieved by the selection of suitable solvents and pressure increase in the packaging material, which causes a supersaturated solution after application by evaporation of solvent fractions

This leads to supersaturation without precipitation in a circumscribed concentration range (Ostwald-Miers range)

The resulting high concentration gradient can be used for improved cutaneous bioavailability of the drug

INTRODUCTION

The application of drugs by means of topicals is a well-established and very frequently practiced form of therapy, especially for skin diseases [1]. The decisive factor here besides the selection of one or more suitable drugs is the right choice of a galenic concept. The choice depends on the physicochemical properties of the skin in the application area as well as on the properties of the drug(s). When developing topicals, the requirements for an appropriate vehicle have to be analyzed precisely. Two aspects must be considered here [2]:

Formulation in the packaging material: It is essential that the vehicle remains chemically, organoleptically and microbiologically stable in the primary packaging material under defined storage conditions (storage stability) and during use (in-use stability) [3, 4]. This requires a vehicle matrix, in which the active substances are incorporated. Ideally, these are then completely or predominantly dissolved. To ensure the chemical stability of the drugs, additional excipients such as antioxidants, buffer substances or solubilizers must often be used, depending on the drug's properties. The concept is primarily oriented towards product stability during production, filling and storage. The vehicle consists of different components that form a three-dimensional molecular order in which the drug is homogeneously distributed. Thereby, this molecular order distinguishes the different galenic concepts and vehicle systems [2]. For example, cream formulations consist of a hydrophilic, a lipophilic and an emulsifier phase. Depending on the quantity and the properties of the emulsifiers used [hydrophilic-lipophilic balance (HLB) values], micelles are formed with an outer hydrophilic (O/W) or lipophilic (W/O) continuous phase. Anhydrous formulations, on the other hand, whose matrices consist of hydrophobic (e.g., fats, oils) or hydrophilic (e.g., polyethylene glycol) components, are called ointments. Gels in turn are formed by swelling of a swelling agent (e.g., hydroxyethyl cellulose or carmellose) and a hydrophilic (hydrogels) or a hydrophobic (lipogels) phase. Furthermore, there is a multitude of modified galenic concepts that are significant for special physicochemical conditions or special indications for application.

Formulation during application: The physical effects of the matrix, mediated during or after application on the skin or in its uppermost layers, are also referred to as the "intrinsic effect" of the vehicle [3]. With the appropriate knowledge of the interactions between vehicle and skin, this intrinsic effect can be used specifically in a therapeutic intervention, e.g., in the form of hydration or occlusion effects. Particularly as the latter are closely linked, moderate occlusion leads to a retardation of the free water phase, which in turn causes an indirect substitution of the bioactive water phase and thus imparts barrier-protective effects. In addition, a lipidization of the stratum disjunctum, i.e., the upper components of the horny layer loosened by the activity of the desquamation enzymes, is caused. Overall, depending on the composition of the lipophilic residue phase, this also has a keratoplastic and keratodilutive effect [5]. After administration, the applied drugs must be available in active form at the biologically defined site of action within the skin, i.e., they must become bioavailable, in order to develop their pharmacological effects. In this process, the vehicle keeps the drug, at least partially, in solution and, by the interaction of its components with the uppermost components of the skin, enables the transit and release of the drug. This mechanism is referred to as the "vehicle function" [2]. The drug penetration rate into the stratum corneum is essentially determined by the physicochemical properties of vehicle and excipients. Depending on the solubility behavior of the drug, hydrophilic and hydrophobic penetration routes can

be defined within the intercorneocytic lipid membranes [6]. By using certain enhancers, the quantitative extent of this transit can be influenced, i.e., promoted, or, if necessary, also retarded. The ideal composition and inner molecular order of a vehicle for a particular drug is essentially dependent on its physicochemical properties, the pharmacokinetic requirements and the conditions of the skin at the site of application. Against this background, the selection of a vehicle system should always be made in the context of the specific clinical treatment situation [2].

This review highlights the basic principles of the galenic concept of supersaturation. For that purpose, it is important to distinguish between the vehicle systems (meaning the semisolid variations of ointments or creams) and the galenic concept (as principle of drug liberation and delivery like supersaturation). This review article does not contain any new studies with human participants or animals performed by any of the authors.

CUTANEOUS BIOAVAILABILITY

To describe the processes during and after the epicutaneous application of a topical, i.e., the processes of cutaneous pharmacokinetics, the influencing factors that determine the cutaneous bioavailability of the drug [2] must be named. The transfer of the drug from the vehicle (donor) into the skin tissue (acceptor) depends on both the concentration of the drug in the formulation and its release rate from the vehicle [6]. The latter is influenced by the binding forces between the drug and the vehicle as well as by its concentration gradient towards the acceptor. The solution state of the drug on the skin surface and the resulting effective concentration, i.e., the thermodynamic activity, play a decisive role. Put simply, only the dissolved portion of a drug is available for transit from the vehicle to the skin. The dissolved portion of the drug is dependent on its solubility properties and the presence of a solvent and, if applicable, solubilizers. All these factors relate to the conditions of the vehicle and can therefore be influenced by the specific choice of physicochemical parameters and a suitable galenic concept.

On the acceptor side, the conditions of the skin at the application site are decisive. Initially, this concerns the visible tissue changes, which are clinically recognizable as efflorescences and are further summarized by acuity state, distribution and dynamics in a defined indication (diagnosis). Changes in the physicochemical properties of diseased skin tissue can also be derived from histopathological phenomena. The altered physicochemical conditions of the skin acceptor can best be derived from the clinicopathological correlation of macro- and micromorphology. Empirically, two extremes can be named here: first, an acute, strongly inflammatory reaction with damage to the physical barrier as a prototype of strongly hydrophilic conditions with low pH (e.g., acute eczema); second, a chronic inflammation with reactive epidermal hyperplasia and an increase of the physical barrier as a prototype of stronger lipophilic conditions (e.g., chronic eczema or psoriasis). However, the dermatopathological spectrum also offers many variations of tissue changes whose effect on the cutaneous bioavailability of epicutaneously applied drugs will not be discussed in detail here.

To understand the processes and relationships one must know that the applied vehicle undergoes a spontaneous restructuring of the inner molecular order immediately after the application and its distribution on the skin surface, which is referred to as metamorphosis—the transition into an effect vehicle (segregation matrix) [7]. This internal restructuring results primarily from a dynamic redistribution of the internal phases, which is driven by the proportional evaporation of the water fraction as well as other volatile components. The resulting molecular interactions within the vehicle matrix can also have an influence on its interaction with the drug. Thus, a change in the quantitative relations within the vehicle can lead to retardation or, conversely, facilitate the liberation of the drug. The derivative change in the functional properties of the vehicle as well as its structural transformation (metamorphosis) justifies the introduction of the term "conversion," which has been extended to include

functional change [2, 7]. The ultimate question, however, is whether the extent of this conversion has a relevant influence on the cutaneous bioavailability of the released drug or respectively, whether the intrinsic effect of the segregation matrix has a useful effect on the therapeutic intervention. Naturally, this cannot be assessed in general, but only in a concrete synopsis of formulation, drug and skin condition.

DIFFUSION

A variety of interactions and forces contribute to the cutaneous bioavailability and ultimately to the effect of individual formulations. Nevertheless, there are general principles based on physicochemical laws that help to categorize the relevant influencing factors. First and foremost, there is the passive transport by diffusion, described by Fick's diffusion law [8]. In a simplified way, it can be stated that the essential force vector from vehicle (donor) to skin (acceptor) is determined by the concentration gradient of the drug Δc between the mentioned compartments. If there is a high concentration of a dissolved drug in the vehicle and its binding forces towards the vehicle allow a relevant release rate (liberation), there will be a directed transit into the skin without external force [2]. Based on Fick's first law of diffusion, the drug transport into the skin can be described with formula (1):

$$J = \frac{D * K}{h} \Delta c \qquad (1)$$

Formula (1): 1. Fick's diffusion law with

J...Diffusionflowofthedrug

D...Diffusioncoefficient

K...Partitioncoefficientskin/vehicle

h...Skinthickness

Δc...Concentrationgradientbetweenskinandvehicle

Assuming that the diffusion coefficient D and the partition coefficient of the drug between the skin and the vehicle K as well as the thickness of the skin h remain constant during application, the quantitative diffusion flux of the drug J is directly proportional to the concentration gradient Δc between the application site and the segregation matrix. The observed dynamics of the process as well as its extent are described with parameters of cutaneous pharmacokinetics and can be determined with standardized models. In addition to the concentration gradient, the uptake of the drug by the skin is essentially determined by its physicochemical properties. These are physically described by the diffusion coefficient. Finally, the application surface is essential for the absolute quantity of drug transfer. Fick's second law of diffusion addresses the relationship between diffusion distance and the time derived from it (diffusion duration). It shows that the relationship between diffusion distance and the duration until isoconces (areas of the same drug concentration) are reached is not linear but increases disproportionately with an increase of the diffusion distance. This relationship is particularly important for indications that are associated with epidermal hyperplasia, and the target compartment of the drugs requires the permeation of the epidermis [5]. In addition to passive diffusion, also other forces contribute to the cutaneous bioavailability of the drug. In this context, the "solvent drag effect" is of practical importance, which describes the co-transport of the drug with its solvent according to the hydrodynamic pressure gradient (Hagen-Poiseuille law) or, in the case of charged drugs, along the electrochemical gradient. Basically, the same conditions apply to the distribution of the drug within the skin organ and its microcompartments. This also shows that the calculation of the absolute drug concentration in a defined target compartment can be very variable and thus requires complex mathematical models. Ultimately, however, clinical proof of the bioavailability of the drug, measured by clinical parameters of efficacy and safety, is required by the regulatory authorities

to evaluate these variable correlations regarding clinical relevance [9].

SUPERSATURATION

Depending on the therapeutic purpose, the physicochemical properties of the drug and the initial galenic conditions, penetration promotion is often needed, i.e., the targeted influence on the release, permeation or penetration of the drug from a topical formulation. Different strategies can be used for this purpose, which can be roughly divided into chemical (penetration-promoting chemicals), biochemical (prodrugs, chemical molecule modification, enzyme inhibition, colloidal system, etc.) and physical procedures (hydration, phono- or iontophoresis, heat input, laser energy input, poration procedures, etc.). In practice, mainly chemical modifications are used, which are selected and optimized depending on the above-mentioned initial conditions [10]. Regarding penetration there are enhancers, accelerants, adjuvants and sorption promoters. The associated substances and their chemical reaction groups are various (e.g., sulfoxides, alcohols, fatty acids, fatty acid esters, polyols, amides, surfactants, terpenes, alkanones or organic acids) [11].

A special form of penetration promotion results from the laws of diffusion when drugs have a limited solubility in inert solvents or the diffusion conditions of the diseased tissue are very unfavorable. To a certain extent, the principle of supersaturation can be used to build up a high concentration gradient for the drug after application [12]. This is achieved by a special state of solution called metastable [13]. When a drug is dissolved in a solvent, a saturation state (saturated solution) is reached under defined ambient conditions. If further drug is added to the saturated solution, it precipitates (phase transformation) and a precipitate is formed. In a semi-solid formulation, the undissolved portion is called a suspension. It is well known that the solubility of a substance is essentially dependent on temperature and pressure [14]. If the temperature and/or the pressure are increased, more drug can dissolve in the solvent until the saturated state is reached [15]. If the heated saturated solution is allowed to cool slowly, within certain limits (so-called Ostwald-Miers range), a supersaturated solution results without the precipitation (crystallization) of the drug (Fig. 1) [16]. We have therefore a thermodynamically metastable solution that only crystallizes if "seed crystals" are added or if the Ostwald-Miers range is left by lowering temperature or pressure. In topicals, the difference between the solubility curve and precipitation curve of the drug can be specifically exploited to increase the concentration gradient of diffusion after application [16]. To maintain these special physicochemical conditions for a sufficiently long time, not only the environmental conditions (temperature and pressure) can be adjusted, but also the composition of the formulation can be modified [17]. This is done by exploiting the conversion of the vehicle at the transition from the application form to the segregation form. By releasing the application form, e.g., from a pressurized primary packaging (spray can), in which the drug is dissolved in a liquid solvent-solubilizer mixture under pressurized conditions, and the aggregate state of

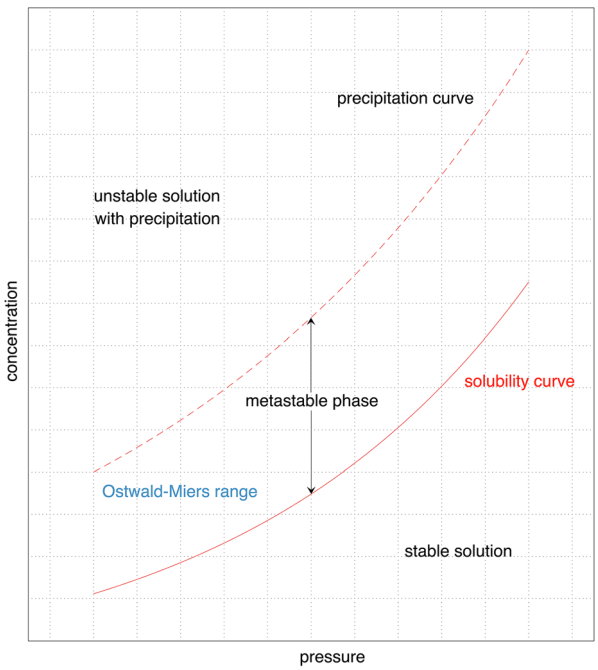

Fig. 1 Schematic representation of the difference between solubility curve and precipitation curve (Ostwald-Miers range)

the solubilizers changes during application (pressure reduction). The resulting foam, whose gaseous components are volatile and thus no longer available for solubilizing the drug in the lipophilic solvent, consequently causes a decrease in the solubility of the drug in the solvent. In the course of supersaturation, an Ostwald-Miers range is formed, which is metastable but causes a supernormal concentration gradient for a limited period of time. This in turn is the basis for an effectively higher bioavailability of the drug in the skin and thus for an increased therapeutic efficacy. However, the latter must be proven in clinical studies in a defined indication. In addition, the possible gain in therapeutic efficacy must be weighed against possibly increased undesired clinical effects.

EXAMPLES FROM PRACTICE

Examples for the use of the principle of supersaturation can be seen in everyday life. For instance hand warmers, so-called "pocket ovens," are a supersaturated solution of sodium acetate trihydrate as a filling in a closed plastic bag. A small metal plate is integrated into the bag, which, when bent, releases particles that act as a crystallization nucleus and thus give rise to the precipitation (crystallization) of sodium acetate trihydrate, which comes with the release of heat. After the exothermic reaction has taken place, the solution can then be returned to the Ostwald-Miers range by applying heat (boiling the bag) and slowly cooling it down, thus enabling it to be used again. Honey, which is a complex aqueous solution of various sugars, can also be liquefied by heating, depending on the sugar content and the sugar spectrum with crystalline content. The honey can be transformed into the Ostwald-Miers range by slow cooling, resulting in a supersaturated, flowable and translucent sugar solution with an intense flavour.

In dermatology, an example of a therapeutic application is the fixed combination of calcipotriol and betamethasone dipropionate as a topical formulation in the form of Enstilar® foam [18]. The two hydrolysis-susceptible drugs are partially suspended in an anhydrous, lipophilic solution and are brought into complete solution by adding a solubilizing mixture of butane and dimethyl ether. The latter are nonpolar, i.e., lipophilic, substances that are gaseous at room temperature and atmospheric pressure. In the primary packaging material (spray can), a homogeneous solution of the medicinal substances is formed under high pressure. During application, the excess pressure causes the lipophilic solution to precipitate and the transfer of butane and dimethyl ether into the gaseous state causes foaming. On the surface of the skin, the solubilizers are volatile and an Ostwald-Miers range is created for both drugs for a limited time, which leads to a high concentration gradient of the drugs between the segregation matrix and the acceptor (skin). This causes a high drug transit. Clinical studies could show an increase in therapeutic efficacy in the indication *psoriasis vulgaris* compared to ointment and gel preparations [19–22]. The latter corresponds galenically to a low-viscous ointment in which betamethasone dipropionate and calcipotriol are partially suspended. Thus, it becomes clear that supersaturation can be an effective principle for dermal drug transport with high practical relevance when used in a targeted manner [23–26]. However, the advantages of supersaturation can also be used to improve the bioavailability, especially of anti-inflammatory drugs, in other dermatoses. For example, the chronic cutaneous lupus erythematosus or verrucous lichen planus offer unfavorable diffusion conditions that can be overcome by supersaturation. It is also conceivable to induce transdermal effects of drugs by supersaturation. In principle, supersaturation can be used for skin lesions with unfavorable diffusion conditions (diffusion coefficient, long diffusion distances, low application concentration of a drug) as an approach to achieve sufficient bioavailability in the target compartment. Unfortunately, this galenic concept has rarely been used in ready-to-use drugs.

CONCLUSION

For topically applied drugs, their cutaneous bioavailability depends highly on the galenic concept of its formulation and not on vehicle system. Supersaturation is a very potent biophysical concept to increase the penetration rate of the drugs due to a higher concentration gradient between the vehicle and the skin. A higher bioavailability of the drug could mean a higher efficacy, which would need to be proven clinically. However, the establishment of more products using that galenic concept could be beneficial for the patients as the therapy would be more effective, resulting in less application frequency and/or a shorter duration of the therapy.

ACKNOWLEDGEMENTS

Funding. Parts of the manuscript were funded by Leo Pharma GmbH, Neu-Isenburg (Germany), as part of an expert review.

Author Contribution. Johannes Wohlrab: drafting the manuscript. Adina Eichner: Corresponding author, concept and design, editing manuscript.

Data availability. The authors confirm that the data supporting the findings of this manuscript are available within the article.

Disclosures. Adina Eichner has nothing to disclose. Johannes Wohlrab has received grants for scientific projects, clinical studies, lectures or consultancy from the following companies in the last 5 years: Abbott, Abbvie, Actelion, Allergika, Almirall, Aristo, Astellas, BayPharma, Beiersdorf, Biogen, BMS, Boehringer Ingelheim, Celltrion, Dermapharm, Evolva, Galderma, GSK, Helm, Hexal, Infectopharm, Janssen-Cilag, Jenapharm, Johnson & Johnson, Klinge, Leo, Lilly, L'Oréal, Medac, Medice, Mibe, MSD, Mylan, Novaliq, Novartis, Pierre Fabre, Pfizer, Regeneron, Skinomics, Stiefel, Wolff.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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