Pentravan® and Pentravan® Plus

The easy-to-use and scientifically-proven effective transdermal vehicle

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Summary

1. TRANSDERMAL DOSAGE FORMS: STATE-OF-THE-ART

1.1 Initial concepts on transdermal drug delivery

Transdermal dosage forms can be understood as dosage forms in which the product is applied to the skin and is diffused through the layers of the skin at a controlled speed, reaching the systemic circulation and being distributed through the tissues until it reaches its site of action.[1] Transdermal dosage forms can be patches, creams, gels, ointments, lotions, gel-creams, plasters and any other pharmaceutical form that allows the active pharmaceutical ingredient (API) to permeate the layers of the skin, resulting in a therapeutic effect.[2]

The transdermal technology gained commercial strength in the 1970s, when new materials (polymers) were developed, which enabled the production of effective systems to promote the absorption of drugs through the skin.[3,4] The development of this new delivery route was stimulated due to the limitations of other conventional drug delivery routes.[5] Advantages of the transdermal dosage forms include:[1,6–9]

- No first-pass metabolism;
- Prevention of gastrointestinal erosion caused by certain drugs;
- Sustained release: lower fluctuations of plasma levels;
- Lower inter- and intrapatient variability: not influenced by gastrointestinal fluids;
- Appropriate for APIs with a (very) short half-life, low therapeutic index and/or low oral bioavailability;
- Patient-friendly: easy to use; simple posology; better adherence for some medicines, especially when there are prominent oral side-effects.

However, some limitations of these systems should also be considered:[10,11]

- Limitation to potent APIs, with low molecular weight (<600 Da);
- Hydrophilic molecules usually have low permeability;
- Difficulty to provide high plasma levels (for APIs that require great doses for clinical effect);
- Unsuitability for APIs that irritate or sensitize the skin, or for allergic patients (e.g., erythema, itching and edema);

In addition to that, the API needs to cross multiple barriers, in order to gain systemic circulation – reason why efficient transdermal vehicles are necessary to help this process to occur in adequate rate.[12–15]

Therefore, developing a transdermal dosage form with proven transdermal permeation is a complex task, which can be challenging to the compounding pharmacies worldwide – reason why ready-to-use vehicles as Pentravan® and Pentravan® Plus are so important. These vehicles can facilitate compounding by the pharmacist, as the final product can be obtained in simple steps (weigh, levigate, and mix). In addition, they are the most studied transdermal vehicles for compounding pharmacies, which assures the safety and efficacy of the products compounded with Pentravan® and Pentravan® Plus.

1.2. Skin structure

For a better understanding on how the transdermal systems need to be designed to achieve maximal clinical effect, it is important to know the physiology of the skin. The skin covers the body surfaces and represents 16% of the body's weight. It has a complex structure, being formed by the epidermis (of ectodermal embryonal origin) and dermis (of mesodermal origin). Just below, there is the hypodermis or subcutaneous cellular tissue. The hairs, nails and glands are functional parts of the skin and called 'skin appendages' (Figure 1).[16,17]

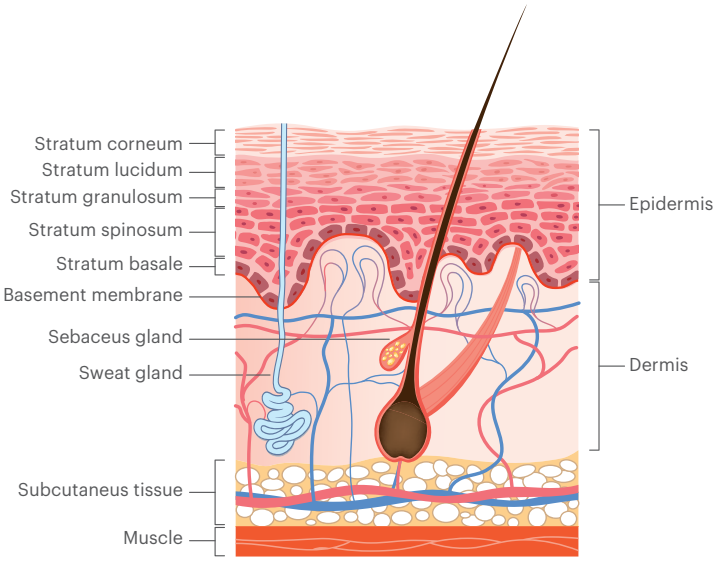


Figure 1. Schematic representation of the human skin.

The functions performed by the skin are multiple, the main being protection against water loss and friction. It also protects against environmental factors such as heat and cold, and microorganisms; it acts as a selective barrier to chemicals; participates in the thermoregulation of the body through its blood capillaries, adipose tissue and glands; contributes to the excretion of substances by sweat; protects against ultraviolet rays due to locally produced melanin and the presence of *trans*-urocanic acid; combined with solar radiation, it transforms synthesized precursors in the organism in vitamin D_3; and sends sensory information about the environment to the central nervous system.[18–20]

The different layers of the skin and their function will be discussed in more detail below.

1.2.1. Epidermis

The epidermis is the outermost layer of the skin and is constituted histologically by keratinized pavement stratified epithelium. Its cells can be divided into corneocytes, also called keratinocytes, and non-corneocytes. Non-corneocytes are: melanocytes, which produce melanin pigment and gives color to the skin; Langerhans cells, which are part of the immune system with the function of antigen-presenting cells, playing a relevant role in local immunological reactions, besides containing corneocytes proliferation; and Merkel cells, which function as nociceptors and are responsible for touch and transmission of nerve impulses of pain through their connection with nerve fibers.[21,22]

Corneocytes, for their turn, are flattened, dead cells without nucleus and with the cytoplasm rich in keratin (an intermediate and amorphous filament protein that gives the epidermis its resistance and impermeability). They are the main cells of the corneal layer, or stratum corneum (SC).[23]

The SC is considered as the main barrier to the passage of chemicals into the body, including APIs. A model proposed to elucidate its structure is called the "model of bricks and cement", as this layer resembles a wall, histologically. In this model, bricks would be corneocytes and cement would be intercellular lipid bilayer, which is composed of ceramides, fatty acids, cholesterol and cholesterol esters.

In addition to this bilayer, there are also the corneodesmosomes, which unite the corneocytes and provide structural stability. This confers enormous cohesion force on the structure, which makes it impossible for most molecules, regardless of their type, to cross it.[24,25]

The SC is continuously renewed, since there is a large amount of epithelial stem cells in the basal layer of the epidermis, which provides surrogate keratinocytes in a period of two to four weeks. The renewal of the epidermis is of the "inside out" type, by a process that involves proliferation of germ cells in the basal layer, differentiation of them in the spinous layer until reaching their degree of functionalization in the granulosa layer, from which cells lose their nuclei when they reach the SC, from where flaking occurs.[20,26]

1.2.2. Dermis

The dermis is composed of connective tissue and serves as a support for the epidermis, functioning as a bond between it and the subcutaneous tissue, or hypodermis. It is richly vascularized and innervated and has a large number of lymphatic vessels. In addition to these structures, it is in the dermis that hair follicles, sebaceous glands and sweat glands are found, although these are considered epidermal appendages, because they have the same embryological origin.[27]

Hair follicles are formed from an invagination of the epidermis; the hairs are inserted into them and protrude to the outer surface of the body. The sebaceous glands are holocrine glands, that is, the formation of secretion comes from the death of their constituent cells. They have ducts that flow into hair follicles and secrete a mixture of lipids that contain triglycerides, free fatty acids, cholesterol and cholesterol esters. The sweat glands are merocrine, that is, they release granules without loss of other cellular material, and secrete the aqueous part of sweat, which also contains sodium, potassium, chloride, urea, ammonia, uric acid and a tiny part of protein. The ducts of these glands flow into the surface of the skin.[17,28]

1.2.3. Hypodermis

The hypodermis is formed by loose connective tissue and is responsible for the union between the dermis and the underlying tissues and organs, albeit in an unseeded manner. That's why it allows a certain slip between the skin and the structures on which it rests. Because it is rich in adipose tissue, depending on the region of the body in which it is located, it provides protection against cold and mechanical shocks, in addition to modeling the body according to the amount of fat it has.[29]

1.3 Routes for APIs penetration into the skin

For a transdermal applied API to become bioavailable and to exert its effect, it needs to:[30,31]

- Dissociate itself from the other components of the formulation and release from the dosage form to reach the skin surface;
- Diffuse to the stratum corneum, deeper layers of epidermis, and dermis;
- Penetrate the capillary vessels or spread through the underlying tissues, in order to gain systemic circulation;
- Reach the site of action and bind to the specific receptors.

Regarding the speed of the process, there are two distinct phases: a slow transposition of the SC and a rapid diffusion through the lower layers of the epidermis and the dermis. In addition, three entrance routes of transdermal substances are considered: the *intracellular, intercellular and adnexal routes* (Figure 2). In the *mixed* route, the substance uses more than one pathway to penetrate.[32]

The *intracellular route* is one in which the drug diffuses cell by cell in the layers of the epidermis. The biggest obstacle to this pathway is the SC, which blocks most substances. In addition, keratin is hydrophilic, which decreases the possibility of absorption of highly nonpolar substances. However, as these cells are present on almost the entire surface area of the skin, this is the most important route, and the transdermal vehicles need to be able to penetrate this keratin barrier to successfully deliver the APIs..[15,33]

When the molecule diffuses through the spaces between cells, through the cellular 'cement', it is penetrating through the *intercellular route*. However, these spaces are limited to 1% of the total skin surface, reducing the probability of absorption by this pathway.[34,35]

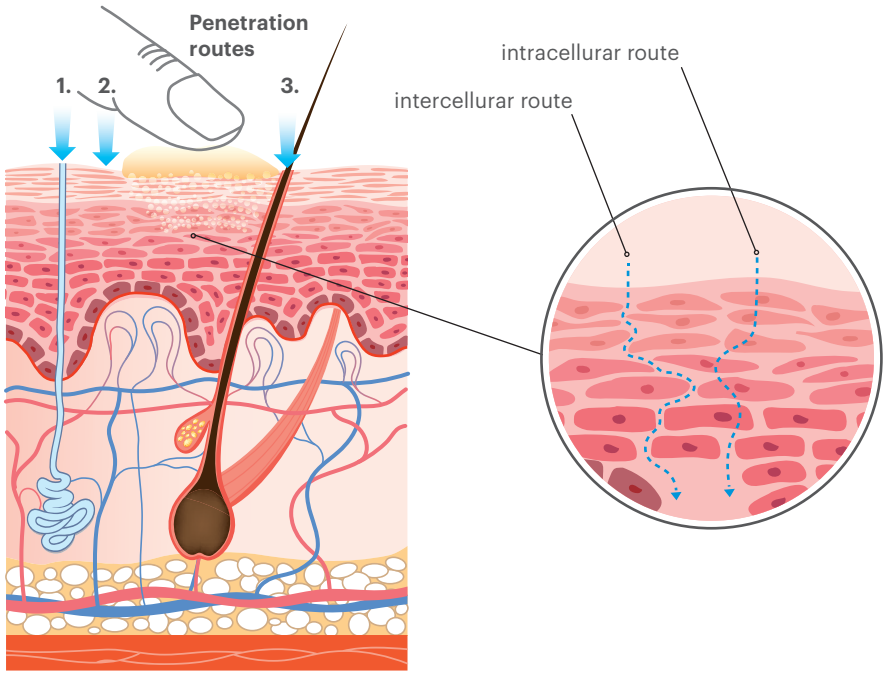


Figure 2. Routes of penetration of drugs through the transdermal route.
1. through the pores of the skin; **2.** through epithelial cells; and **3.** through hair follicles.
In particular (right figure), the possibility of intercellular and intracellular transport.

Another possibility of absorption is through epidermal appendages (hair follicles, and sebaceous and sweat glands - *adnexal route*). In this way, charged drugs or drugs with a higher molecular mass can penetrate, provided they have an appropriate oil/water partition coefficient. However, also in this case, the total area is limited to around 0.1%. In addition, there is great variability in the density of the annexes over the body, making specific application complicated.[18]

For example, although a higher concentration of hair follicles increases the probability of absorption, hair can also act as a physical barrier to the passage of the API. Regions with high density of thick hair have therefore a low penetrability potential.[36] There are other factors that can interfere with penetration through the transfollicular route. Sebum synthesized by the sebaceous glands for example, could have an interaction with the APIs or impact their physicochemical properties and hence influence the penetration.[37]

1.4. Penetrating determinants

The physicochemical properties of the drugs determine their route and degree of absorption. Among them are the APIs' pKa, molecular size, oil/water partition coefficient and stability within the formulation. Additionally, the location where the cream is applied and the bonds the API is making with the epidermal components that it finds in the path will also influence the absorption. It is known, for example, that drugs in their non-ionic form have greater permeation capacity than those in dissociated form. This is not limited to hydrophilic APIs, as amphyptic molecules can also permeate promptly.[13,38,39]

High-weight molecules are more difficult to be administered through this pathway. Although the ideal molecular size is debatable and size is surely not the only crucial factor in the process, it is generally recommended that substances have a molecular weight less than 600 Da[18], preferably even 400 Da.[32,14]

Another crucial driver is the thermodynamic potential. The greater the difference in concentration between the vehicle and the skin, the higher the potential and hence, the greater the drive into the skin.[40]

Additionally, the pH of the formulation also influences with permeability, as the pH can ionize weak acids and bases and reduce permeation.

In addition to the pH of the formulation, the pH of the skin (~ pH 6 in adults) also interferes with the degree of ionization of the compound, both of which should be taken into account.[41]

Another factor influencing the bioavailability of transdermal delivery of APIs are the enzymes which are abundantly present in the skin. These enzymes can metabolize APIs, since they catalyze both phase I and phase II reactions.[42]

A phenomenon that deserves attention is the accumulation of substances in the SC. This occurs with certain drugs that forms precipitated complexes with keratin, through the binding of this hydrated molecule with the polar groups of the drug. From these reservoirs, part of the drug is released at a much slower pace, leading to a decreased ability to withdraw the drug from the system as soon as undesirable effects are noticed.[43]

When there is no formation of drug reservoirs in the corneal layer, the absorption of the drug follows Fick's diffusion laws. According to Fick's first law, the steady-state flux of diffusion of the API, which can be deducted from the following equation:

$$J = K_P \times \Delta C = \frac{P \times D \times \Delta C}{e}$$

where J = steady-state flux (μg/cm^2/h), K_P = permeability coefficient, ΔC= concentration differential between the two sides of the membrane (C1- C2), P = coefficient of partition between stratum corneum and vehicle, D = diffusion coefficient (cm^2/s), and e = skin thickness (μm).

D can be defined as:

$$D = \frac{e^2}{6T_L}$$

where T_L is the lag time.

In some situations, the drug has a higher affinity for the transdermal formulation itself than for the skin tissue, and hence the absorption is very slow and not obeying Fick's laws. In these cases, different mathematical models can be used: cumulative amounts of drug diffusion per unit area (μg/cm^{-2}) are plotted against time (h) for zero order kinetics; cumulative amounts of drug diffusion per unit area (μg/cm^{-2}) are plotted against square-root of time ($\sqrt{h}$) for Higuchi model (pseudo-first order kinetics); log of the cumulative amounts of drug diffusion per unit area (log μg/cm^{-2}) are plotted against time (h)

for first-order kinetics; and cubic root of the unreleased amounts of drug per unit area ($\sqrt[3]{\mu g/cm^{-2}}$) are plotted against time (h) for Hixson-Crowell model.[45]

However, mathematical models are still insufficient to fully model transdermal absorption, since numerous other factors intrinsic to the patient and the environment are impacting the absorption process. Among these factors, the patient's age stands out (the children's skin is the most permeable, and permeability declines with age). Other factors include: temperature, relative humidity (the higher the humidity, the greater the permeability), the patient's sex (male's skin has decreased penetrability compared to female skin), the diet followed by the patient, the degree of skin hydration, skin diseases, concomitant intake of medications, and the lipid degree of the skin.[46] When zooming in on the temperature, an increase in the transdermal system and skin temperature will result in an increased permeation. This is the result of an increased peripheral circulation in the region where the formulation is applied, dilatation of the underlying vessels and the resulting elevated absorption.[47]

1.5 Optimization of permeation of APIs from transdermal dosage forms

Because of the many determinants in the transdermal delivery, certain APIs can require additional modifications to ensure sufficient bioavailability from a transdermal dosage form. Some of the possible strategies are briefly explained here.

Chemical methods	Physical methods
• Chemical permeation enhancers	• Iontophoresis
• Prodrugs	• Sonophoresis
• Ion pairs	• Electroporation
• Eutectic systems	• Magnetophoresis
• Liposomes and analogues	• Microneedles

1.5.1. Chemical methods

Permeation enhancers

Absorption promoters or permeation enhancers are substances added to transdermal formulations in order to increase the flux of drugs through the skin, primarily through the SC.[48–50] Among the known substances that are used for this purpose, the most important are: water, hydrocarbons, sulfoxides (mainly dimethylsulfoxide - DMSO), fatty acids, amides (such as urea and its derivatives), essential oils, terpenes and derivatives, epidermal enzymes, pyrrolidones, surfactants, polyols, esters, diethylene glycol monoethyl ether (Transcutol®), propylene glycol, isopropyl palmitate and alcohols.[18,51–53]

The mechanism of action of these substances is variable. DMSO and decilmethylsulfoxide, for example, interact with keratin present in corneocytes and make its structure looser, making the corneal layer more permeable.[54] DMSO also establishes a reservoir of non-polar substances that are usually poorly absorbed in the SC, favoring their absorption. Other solvents, such as propylene glycol and ethanol, can alter the chemical environment of SC and alter the solubility characteristics of lipids, allowing a second molecule to be partitioned more easily by it.[18]

Surfactants are an important class of compounds that have been used for some time for this purpose. They promote a reduction of surface tension and reversibly denaturate skin proteins, increasing the absorption of substances. However, they can cause skin irritation, which is directly proportional to the extent of skin penetration. Cationic surfactants are more irritating than non-ionic ones. This class includes: sodium lauryl sulfate, sodium docusate, polysorbates and laurocapram.[55–57]

As several of these substances can cause skin irritation when added in concentrations necessary to exert its effect of promoting penetration,[14,48,49] and ideal promoter is the one that in addition to promoting the permeation of drugs through the skin is pharmacologically inactive, nontoxic and promotes the hydration of the epidermis.[18] As finding a single molecule with all this characteristics is challenging, a trend is to combine multiple promoters at low concentrations for a synergistic effect.[58,59]

Prodrugs

If the API that is intended to be applied by the transdermal route does not present the ideal physicochemical characteristics for such a pharmaceutical form, the use of a prodrugs can be considered. These are pharmacologically inactive substances derived from the original drug, but with changes in its molecule that allow its transport through the epithelial layers, optimizing the partition of the drug. After the permeation process, the enzymes present in the body would activate the prodrug through reactions that would release the original drug, converting it into an active molecule capable of exerting the desired effect on the body.[18]

Ion pairs

APIs consisting of electronically charged molecules do not transpose the SC promptly. A strategy aimed at permeating these drugs is the formation of ionic pairs through the addition of a species loaded with electronic charge contrary to that of the active ingredient. The neutral complex, being lipophilic, would then cross the SC and dissociate itself into the lower tissues. Experiments have shown that the increase in permeation is modest, but useful when the addition of chemical promoters is not feasible.[60–62]

Eutectic systems

Some studies suggest that the use of eutectic mixtures in formulations can lead to an increase in the drug flux through the skin, e.g., lidocaine-menthol system or propranolol attached to saturated or polyunsaturated fatty acids.[63,64]

Liposomes and analogues

Liposomes are liquid particles that have the ability to envelope pharmacologically active molecules and release them into the skin. Because these are large particles to cross the intact epidermis, the aim is generally to have a local delivery of the APIs, which should then permeate through the cells.[11,65,66]

When surfactants such as sodium cholate are added to liposomes, a particle called transfersome is formed. These vesicles are ultradeformable and can stretch through SC pores and permeate the epidermis. As transfersomes act under hydration gradiente (when applied under the skin, the water begins to evaporate and they then follow the flux of the dry surface of the skin to the internal aqueous tissues), it is necessary to work in non-occlusive conditions (i.e., a semi-solid formulation is better than a transdermal patch).[67,68]

Other modified liposomal particles can also be used to improve the drug flux through the skin. Examples include: ethosomes (liposomes with high ethanol content that release drugs to deep regions of the skin or to systemic actions), and niosomes (which use non-ionic surfactants to form vesicles).[69–71]

1.5.2. Physical methods

Iontophoresis

This technique is defined as the application of an electrical potential that maintains a constant electrical current through the skin. Using two electrodes on different locations on the skin and a weak current in the order of milliamperes, a circuit is created. As a result, normally uncharged molecules are charged and the current propels the electrically charged molecule through the skin, without causing pain or irritation.[72–74]

Sonophoresis

Adjuvant to the topical application of the drug, via transdermal patch or other topical pharmaceutical forms, an ultrasound device can be used to increase drug flux in a method known as sonophoresis. Low frequency ultrasonic waves cause lipid disturbances in the cell membranes of corneocytes. Thus, microcavities are formed that help in the drug flux to the deepest strata of the epidermis. In addition, the micro-vibrations in the epidermis caused by ultrasonic waves, increase the kinetic energy of the molecules in the topical preparation.

Sonophoresis makes use of all 3 mechanisms: acoustic cavitation, acoustic microflow and heat generation. Cavitation is the formation of very small air bubbles in the liquid in contact with ultrasonic waves. Microflow is closely related to cavitation, favoring the dissolution of suspended particles and a higher concentration of drug available for absorption physically close to the skin. Heat generation can occur both on the surface and in the deeper layers of the skin. Its greatest limitation is the fact that it is specific for use in a doctor's office, due to the need for an ultrasound source.[75]

Electroporation

The electroporation or electro-permeabilization is the application of rapid electrical pulses of approximately 100-1000 volt per cm of skin, which leads to the formation of transient aqueous micropores in the membranes of epithelial cells. These aqueous micropores act as shortcuts for the drug, so the API does not have to cross the corneal layer. Synthetic molecules and small macromolecules (< 10 kDa) are particularly suitable to be transported by this method.[76–78]

Magnetophoresis

Static magnetic fields can be used to transport diamagnetic materials through the skin, which occurs by the probable modulation of SC by these magnetic fields.[79,80] In practice, the formulation will include magnetite particles homogeneously dispersed to form magnetoliposomes, which are directed to the target tissue as the vesicles are repelled by the magnetic field generated on the surface of the skin.[81]

Microneedles

This method involves the use of very small (micrometer scale) massive or hollow needles. Microneedles are generally used to potentiate the transdermal transport of substances through the formation of micropores in the skin. In the case of solid microneedles, the APIs are contained in adhesives and can be absorbed at the local or systemic level. When using hollow microneedles, the drug is directly injected into the patient's skin.[82–84] Both methods result in superficial skin penetration and, therefore, do not reach nerve structures and hence these injections are pain-free.[85]

2. PENTRAVAN® AND PENTRAVAN® PLUS: THE READY-TO-USE VEHICLES

From the previous section, one could see that the permeation process for an API involves a series of multiple mechanisms that need to be evaluated for a proper transdermal product.

To facilitate transdermal administration and improve safety and efficacy, Fagron has developed Pentravan® and Pentravan® Plus, two ready-to-use vehicles that can be easily incorporated in compounding pharmacies routines.

The main benefit of the Pentravan® vehicles is their proven permeation efficacy over a wide range of different APIs. The bioavailability of the API and the resulting therapeutic effect are the consequence of the permeation from the vehicle used. Therefore, permeation studies are a good tool to get insight in what percentage of the API will reach the bloodstream and exert its effect. As yet, no transdermal vehicle has been more intensively studied then Pentravan®.

2.1 Differences between the vehicles

Pentravan® is a penetration enhancing vanishing cream that acts as a transdermal delivery system for APIs and is intended for use as a cream base for pharmaceutical compounding. It is ready-to-use to facilitate compounding by the pharmacist. Pentravan® is an oil-in-water emulsion capable to establish a greater rate and extent of absorption of the API than other transdermal bases. Therefore, more of the API will become available in a shorter time to establish the effect of the therapy. Besides that, Pentravan® is a true vanishing cream, leaving no sticky residue and providing a cosmetically elegant skin feel. Therefore, there is no need to cover the area of application to prevent transferring of the cream and to ensure effectiveness of therapy. It is preserved and fragrance-free.

After application on the skin, the API molecules that are dispersed within Pentravan® are released and able to penetrate the SC. Once through the SC, drug molecules may pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the systemic circulation.

Pentravan® Plus is a related vehicle and is a higher viscosity version of Pentravan®. It uses the same technology as Pentravan®, but with additional emulsifiers to allow for incorporation of higher concentrations (>25%) of APIs and solvents. This stablishes greater loading capacity for APIs than alternatives, which makes it possible to compound creams with higher concentrations and more than one API when needed.

Pentravan® Plus vanishes into the skin, enhancing penetration of the APIs without leaving a sticky residue on the skin. Therapeutic compliance and patient satisfaction therefore can be significantly improved with Pentravan® Plus.

The composition of Pentravan® Plus in terms of permeation enhancers is the same as Pentravan®, therefore the results from studies conducted with Pentravan® can be extrapolated to Pentravan® Plus.

In addition, the key points for both vehicles are:

- Ready-to-use vehicles.
- Timesaving: no need to weigh and mix multiple ingredients.
- Simple compounding process.
- Compatible with a broad range of APIs.
- Allows for individualized therapy and more accurate dosing.
- Proven effectiveness and reproducibility of transdermal penetration of APIs.
- Elegant skin-feel. Non-greasy, vanishes quickly. Fragrance-free.
- Decreases losses on dose during application and contamination of third parties (e.g. children or family members) through physical contact.
- Patient friendly.
- Patient groups: suitable for all patient groups.
- Adverse reactions: none recorded; possible.

2.2 Safety profile

Pentravan® and Pentravan® Plus are formulated without:

- Parabens
- Formaldehyde donors
- Benzyl alcohol/benzyl benzoate
- Triclosan
- Para aminobenzoic acid
- Boric acid
- Mineral oil and petrolatum
- Peanut oil
- Lanolin
- Sodium lauryl sulfate
- Ethoxylates and 1,4-dioxane
- Propylene glycol
- Fragrances and dyes
- Phthalates
- Nitrosamines

2.3 Technical Specifications

	Pentravan®	Pentravan® Plus
Visual Appearance	Stiff, yellowish to beige cream; slight odor of lecithin.	Stiff, yellow cream; slight odor of lecithin.
Yield Value	53 - 108 Pa	> 120 Pa
pH	Between 4.0 and 6.0	Between 3.5 and 5.5
Phase separation with APIs	No phase separation after compounding.	No phase separation after compounding.
Color change with APIs	No color change after compounding.	No color change after compounding.
Assay of Preservatives	Benzoic Acid, 0.19% – 0.27%, Sorbic Acid, 0.17% - 0.33%.	Benzoic Acid, 0.19% – 0.27%, Sorbic Acid, 0.17% - 0.33%.
Microbiology	Total Aerobic Bacteria Count (TAMC) < 10^2 cfu/mL Total Yeasts and Molds Count (TYMC) < 10^1 cfu/mL *S. aureus*: absent/1g *P. aeruginosa*: absent/1g	Total Aerobic Bacteria Count (TAMC) < 10^2 cfu/mL Total Yeasts and Molds Count (TYMC) < 10^1 cfu/mL *S. aureus*: absent/1g *P. aeruginosa*: absent/1g

2.4 Studies

Pentravan® has been more extensively studied than any other transdermal vehicle. The studies conducted to date are briefly discussed in the following section. All permeation studies were conducted in concordance with the European[86] and United States guidelines.[87] As the passage of an API from the SC to the systemic circulation is generally the limiting step for percutaneous penetration, *in vitro* permeation studies are considered indicative for the clinical effect in patients.[86] In the *in vitro* studies, the release rate measured is indicative for the combined impact of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form.[87]

3. ENDOCRINOLOGY

3.1. Hormone replacemente therapy

Bioidentical hormones (or simply hormones, such as testosterone, estradiol, estriol and progesterone) present low oral bioavailability. In addition, their physicochemical properties make them exceptional candidates for transdermal application, as they can easily diffuse through the human skin, notably because of their low molecular weight and adequate lipophilicity.[88]

The decrease in hormone levels throughout life is physiological, both in men and women, as part of aging. Specifically, in women this occurs due to the progressive decrease in ovarian activity, since the ovary is responsible for the secretion of the so-called female hormones, especially estradiol, estrone and estriol. These changes accompany the transition between fertile and non-fertile periods of life.[89] However, this decrease can occur so abruptly and intensely that it tends to lead to conditions considered pathological. Some clinical symptoms observed as a result of this hypo-estrogenism and that are of special interest from a medical point of view are: (i) trophic changes of the skin and vaginal mucosa, characterized mainly by the atrophy of the labia majora and the alteration of the hair pattern the vulva, in addition to decreasing the thickness of the vaginal epithelium and dryness of the vaginal mucosa; (ii) tendency to osteoporotic fractures due to accelerated loss of bone mass; (iii) psychological disorders such as loss of libido and insomnia; (iv) modification of the lipid profile, such as an increase in the levels of triglycerides and low-density lipoprotein (LDL), and a decrease in those of high-density protein (HDL, high-density lipoprotein); and (v) hot flushes, understood as the sudden waves of heat that pass through the body. The set formed by all these biological changes constitutes what is called climacteric, conceptualized as the transition phase between the reproductive and non-reproductive phase in women due to the depletion of ovarian follicles and the consequent decline in the production of estrogens - which in the end leads to the menopause. This, in turn, is understood as the time point at which menstruation stops completely.[90–92]

The transdermal route for hormones presents some advantages over other delivery routes:[93,94]

- Hormones have good skin permeability,
- Prevents the synthesis of liver proteins resulting from the first pass metabolism,
- Transdermal estradiol does not increase C-reactive protein,
- Lower risk of thromboembolism,
- Transdermal administration of estradiol produces lower levels of estrone than the oral route,
- Transdermal testosterone promotes less risk of polycythemia,
- Percutaneous estradiol and testosterone have high tolerability and few adverse effects,
- Transdermal administration of testosterone restores T levels while maintaining estradiol levels in the physiological range.

A good comparison of the oral and transdermal use of hormones can be seen in Figure 3A. Oral. As observed, oral route can lead to hormone serum peaks, while transdermal use provides a much more sustained release throughout time. In Figure 3B. Transdermal, it can be observed that the semi-solid transdermal dosage form provides more stable serum concentrations of hormones even compared to patches and sprays, over a 24h period (Figure 3C).

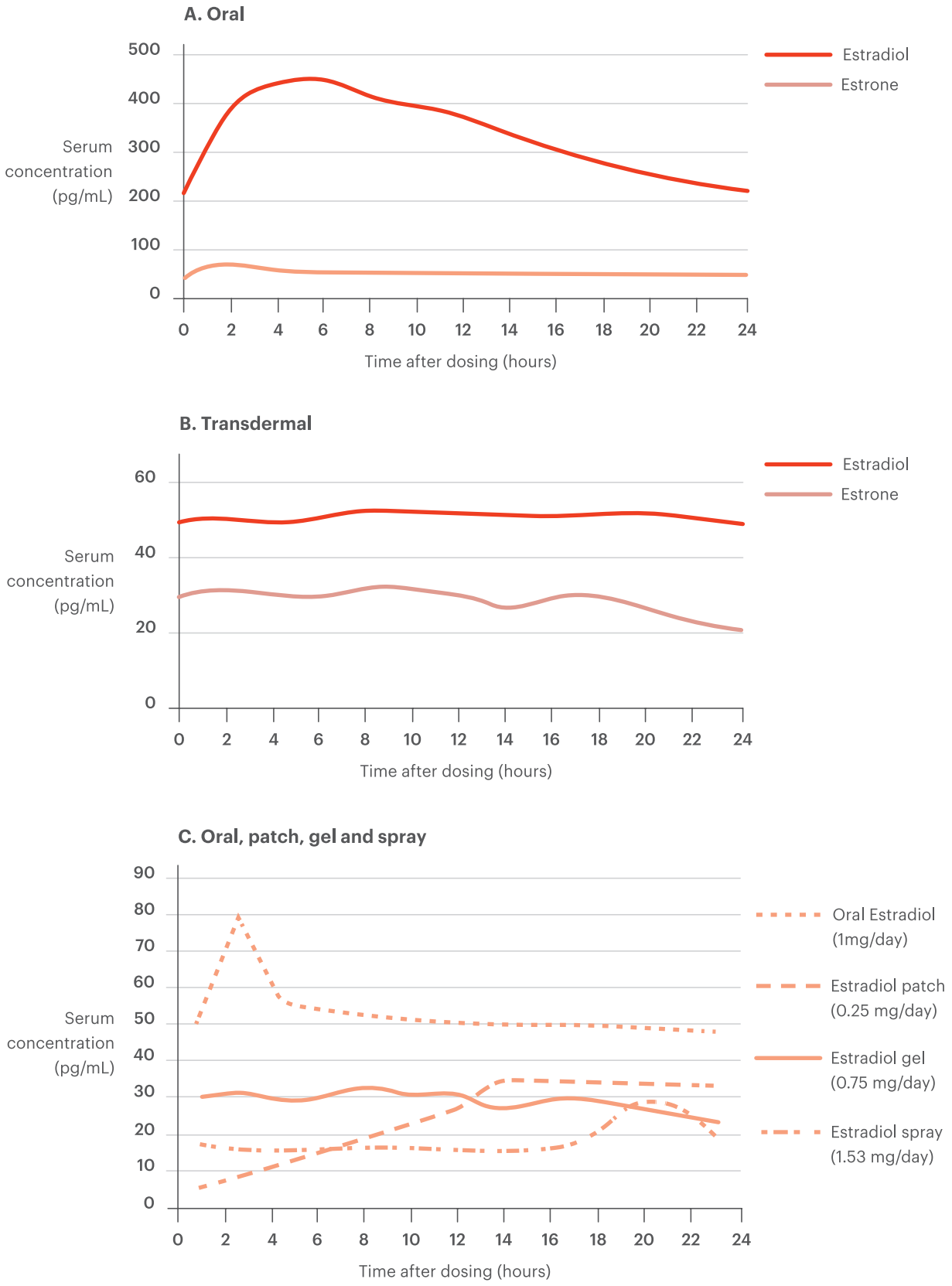


Figure 3. A. Comparison of estradiol and estrone serum levels after oral and transdermal administration. B. Comparison of estradiol serum concentration after oral and various transdermal (patch, gel and spray) modes of administrations. Adapted [95].

• **Study**

In vitro percutaneous absorption of ketoprofen and testosterone: comparison of pluronic lecithin organogel vs. Pentravan cream.
International Journal of Pharmaceutical Compounding. Vol. 16, n. 3, p. 248-252, 2012.[96]

In this study, the objective was to directly compare the penetration characteristics of Pentravan® with that of the traditional transdermal vehicle used by that time (PLO, Pluronic Lecithin Organogel).
Two drugs were used: ketoprofen (100 mg/g) and testosterone (100 mg/g). The results showed that with Pentravan® the penetration was increased for both compounds - 3.8-fold higher for ketoprofen (Figure 4) and 1.7-fold higher for testosterone (Figure 5).

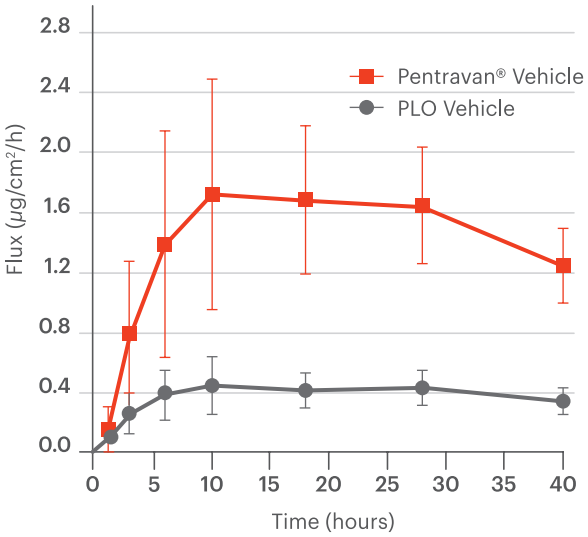


Figure 4. Meanflux (mcg/cm²/hr) results: Ketoprofen. (Mean ± SEM).[96]

• **Study**

Transdermal formulations containing human sexual steroids: development and validation of methods and in vitro drug release.
Química Nova. Vol. 37, n. 4, p. 720-727, 2014.[97]

The objective of this study was to develop quality control methods for testosterone (50 mg/g), estradiol (1.0 mg/g) + estriol (4.0 mg/g), and progesterone (50 mg/g) in Pentravan®. It also evaluated the drug release of these hormones from the vehicle, an important check to assure the APIs can diffuse from the formulation to the skin surface (so the permeation will occur). The conclusion of the study was that the vehicle (Pentravan®) exhibited high releases rates of incorporated hormones, proving to be an optimal option for transdermal route.

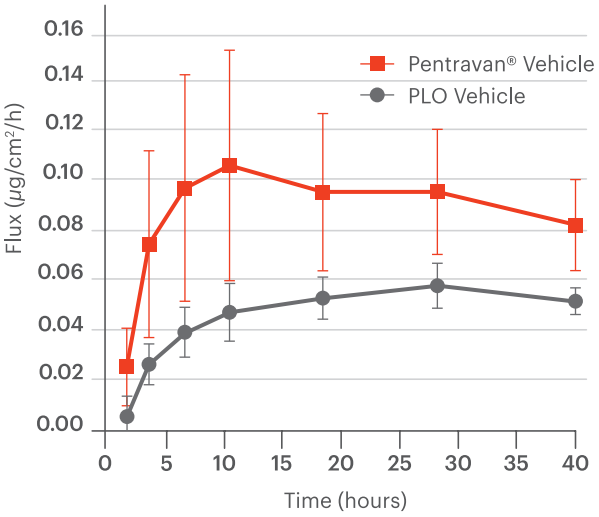


Figure 5. Meanflux (µg/cm²/h) results: Testosterone. (Mean ± SEM). [96]

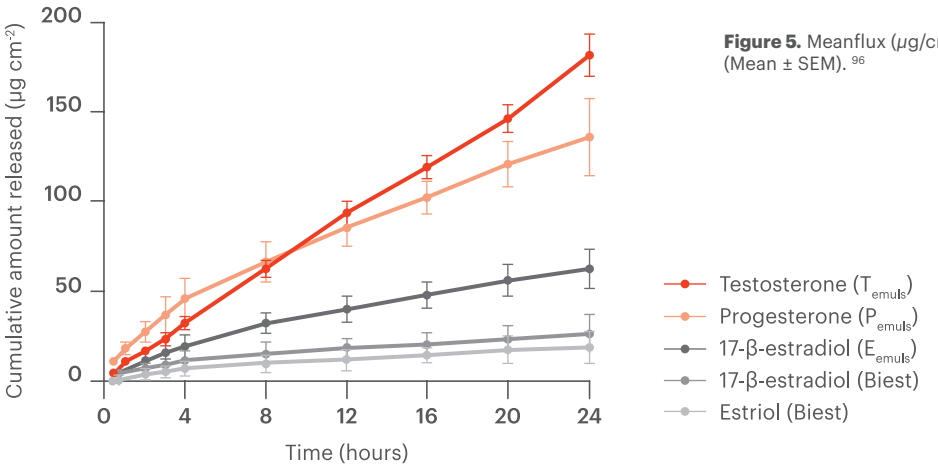


Figure 6. Release profiles of human sexual hormones. Results are presented as mean ± standard deviations (*n*= 6).[97]

• Pentravan® **Study**
Evaluation of Percutaneous Absorption Performance for Human Female Sexual Steroids into Pentravan Cream.
International Journal of Pharmaceutical Compounding. Vol. 18, n. 4, p. 332-340, 2014.[98]

The purpose of this work was to evaluate the permeation performance of Pentravan® cream for transdermal delivery systems containing progesterone (P) 50 mg/g, estradiol standalone 1.0 mg/g, and estradiol associated with estriol, 1.0 and 4.0 mg/g, respectively. The experiments were conducted to mimic pulsatile therapy (48h use).
The results of the study showed that the vehicle was able to provide percutaneous absorption rates compatible with clinical treatment needs. Permeation percentages per dose obtained were: 76.8% for progesterone; 99.9% for estradiol standalone; and 84.7% for estradiol and 49.9% for estriol (lag time = 2.00), in combination (Figure 7). Drug fluxes (in µg/cm²/h) were 4.55 for progesterone; 1.15 for estradiol standalone and 1.13 for estradiol + 0.27 for estriol in combination. The conclusion was that human female sexual hormones incorporated in the oil-in-water vanishing cream base and applied topically are expected to exert their biological activities systemically with good efficacy due to their satisfactory permeation through human skin.

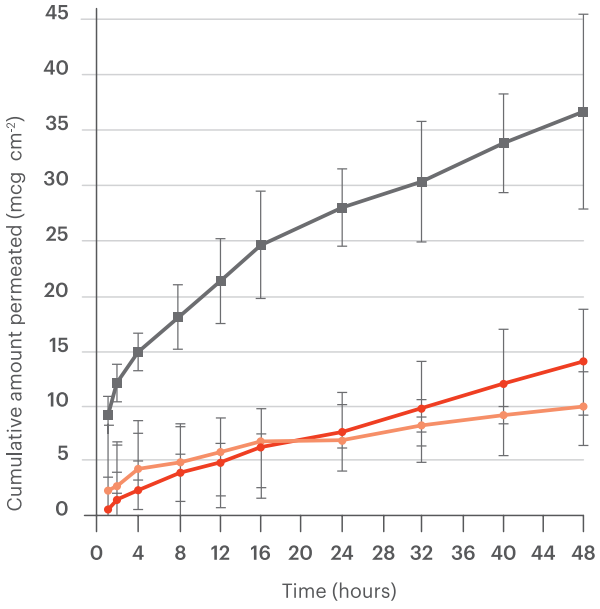


Figure 7. *Ex vivo* permeation profiles of human sexual hormones through excised human skin. Results presented as the mean ± standard deviation (*n*= 6).[98]

• **Study**
Transdermal Oxandrolone: Ex Vivo Percutaneous Absorption Study.
Current Drug Delivery
Vol. 14, n. 5, 0. 696-700, 2017.[99]

Oxandrolone is a synthetic testosterone analogue, which shows strong anabolic properties and weak androgenic activity – therefore, not a bioidentical hormone. As oral oxandrolone can has several adverse effects, and the transdermal route can potentially avoid or minimize these adverse effects, the objective of this study was to evaluate the permeability of oxandrolone (20 mg/g in Pentravan®) in human skin for possible transdermal application as an alternative to oral treatment. The experiments showed that a significant percentage of the total amount of drug (247.6 µg or 25.9% of the applied dose) is delivered (Figure 8).

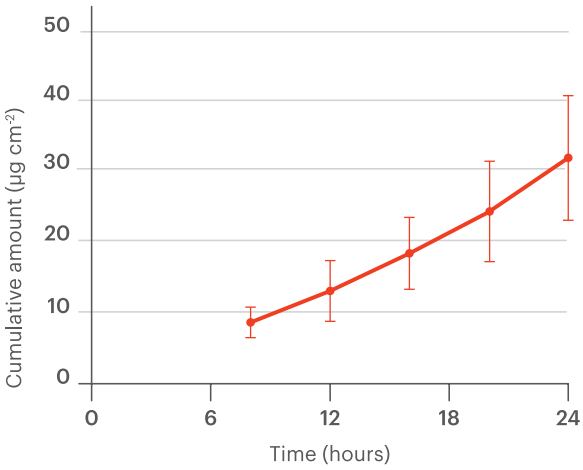


Figure 8. Cumulative amounts of oxandrolone qualified into the receptor medium: *ex vivo* percutaneous absorption profile. Results presented as mean ± standard deviation (*n*= 6).[99]

Oxandrolone therefore seems and interesting candidate for transdermal delivery. In comparison, after an oral dose of 10 mg, a 70-kg man with 40 mL of plasma per kg would absorb an estimated 1,167.6 µg of oxandrolone, whereas after transdermal application, 2,590 µg of the same dose would be absorbed.[100] In this sense, transdermal oxandrolone could be a viable alternative for traditional oral form, as it bypasses the first-pass effect.

4. AGING

Aging-related diseases are among the leading causes of death in industrialized countries. Protocols for aging can be considered in two main strategies: dermatology/cosmetology, dealing with the aesthetics of the patients; and systemic treatments that could play a role in different systems related to the multiple aging pathways. Studies with Pentravan® have been focused on resveratrol and monomethylsilanetriol (for their effects on skin, hair and nails) and metformin and desmopressin (involved in regulation of metabolic and cellular processes).

4.1 Resveratrol

Resveratrol (3,5,4-trihydroxystilbene) is a non-flavanoid phenolic compound produced by some spermatophytes (such as grapes), reason why it is found in high concentrations in red grape skins and their wines.[101] The main active isomer, *trans*-resveratrol, is a molecule of high interest for anti-aging skincare products, due to its potent antioxidant activity. In addition to the antioxidant potential, it also presents neuroprotective, anti-photoaging and antiviral activities, and it seems to also play a role in the prevention and reduction of pathological processes such as inflammation, cancer and heart diseases.[102]

Despite its interesting potential, resveratrol presents low oral bioavailability, due to its extensive metabolization.[103,104] Because of that, an increasing number of studies dealing with topical and transdermal delivery of resveratrol has been conducted, for anti-proliferative and chemo-preventive against skin carcinogenesis,[105] sun protection against skin damage from ultraviolet B,[106] and antimicrobial effect against dermatophytes and herpes simplex virus.[107,108] Transdermal delivery of resveratrol is also gaining momentum as an alternative to achieve systemic levels.

- **Study**

In vitro drug release and ex vivo percutaneous absorption of resveratrol cream using HPLC with zirconized silica stationary phase.
Journal of Chromatography B. Vol 947-948, p. 23-31, 2014.[109]

From the initial dose applied, 62.6% of the API was able to cross the skin and reach the receptor medium. From these results, it can be calculated that a 20 mg resveratrol dose, topically applied, would theoretically be equivalent to a bioavailable dose of 12.53 mg (Figure 9).

In comparison, the oral bioavailability of resveratrol is lower than 1%.[110]

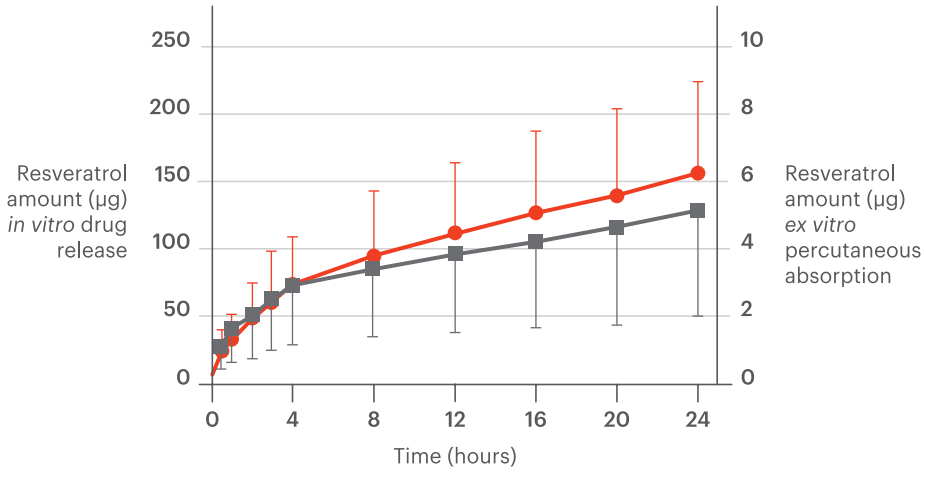


Figure 9. Cumulative amounts of resveratrol qualified into the receptor medium: (●) *in vitro* drug release profile and (■) *ex vivo* percutaneous absorption profile (results presented as mean ± standard deviation, *n*= 6).[109]

• Study

Studies with Emulsion Containing trans-resveratrol: in vitro Release Profile and ex vivo Human Skin Permeation.

Current Drug Delivery. Vol. 12, p. 157-165, 2015.[111]

In a second study, a similar result was found. Of the applied dose, 64.96% was able to permeate the skin and reach the receptor medium (Figure 10). The trans-resveratrol release kinetic followed the Higuchi's model with steady-state diffusion flux and lag time of 138.5 µg/cm²/h and 0.49 h, respectively. The article therefore concluded that trans-resveratrol may be able to exert its biological activity systemically when applied via transdermal emulsion, due to its good flux rate and its high retention in viable skin layer.

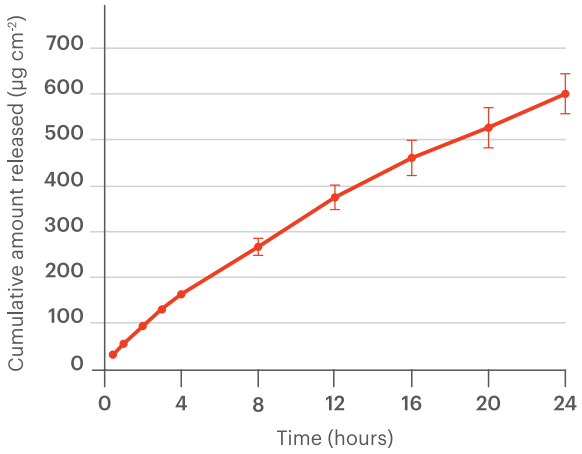


Figure 10. *In vitro* release profile of trans-resveratrol within the transdermal emulsion (mean cumulative amount ± standard deviation.[111]

• Study

Activators of SIRT1 in wound repair: an animal model study.

Archives of Dermatological Research. Vol. 311, p. 193-201, 2019.[112]

The aim of this study was to evaluate the effects of caloric restriction (CR) and resveratrol, as activators of SIRT1, in the healing of excisional skin wounds on the dorsum of rats. The authors used different strategies, such as CR and topical resveratrol, compounded using Pentravan®. The conclusion was that both CR and resveratrol (in Pentravan®), act as activators of SIRT1, and could positively modulate the repair of tissue wounds, due to the induction of angiogenesis, fibroplasia, and collagen organization.

4.2 Silicon (monomethylsilanetriol)

Silicon (Si) is one of the most abundant element in the Earth's crust; obtained from the diet (e.g., plant-based foods), it can be found in the human body in all tissues, specially the connective tissue.[113] The progressive reduction of Si body levels can affect the synthesis of collagen by the fibroblasts, as well as the activations of dermal collagenase.[114] The supplementation of Si can play a role in this process, and also in promotion of the synthesis of elastin; stimulus for nail hardness; increase of resistance and thickness of hair fiber; and preservation of blood vessel elasticity – depletion of Si also affects the synthesis of glycosaminoglycans in bone and cartilage.[115]

In spite of its importance, the chemical form of Si determines its absorption and bioavailability. For example, particulate and polymerized forms exhibit minimal oral absorption and bioavailability, while monomers (orthosilicic acid and organic compounds such as monomethylsilanetriol, MMST) may be well absorbed.[116]

MMST is the active substance contained in SiliciuMax®. It is a colorless and odorless liquid. A clinical study showed that SiliciuMax® provides significant improvement of facial wrinkles and UV spots. Changes were also observed at the end of the study in skin texture and length of the eyelashes. Additionally, hair aluminum levels decrease with the treatment, suggesting that the absorbed Si can play a role in detoxification processes.[115]

• Study

Topical monomethylsilanetriol can deliver silicon to the viable skin.

International Journal of Cosmetic Science. Vol. 41, p. 405–409, 2019.[117]

The objective of this study was to assess whether monomethylsilanetriol (MMST, SiliciuMax®, a source of organic silicon) can present Si, when applied topically as a transdermal cream. A significant percentage of permeation was found.

Almost 60% of the applied dose could be considered as active drug. This makes the transdermal route a good option for the delivery of organic silicon to the systemic circulation and the local site where the product was applied.

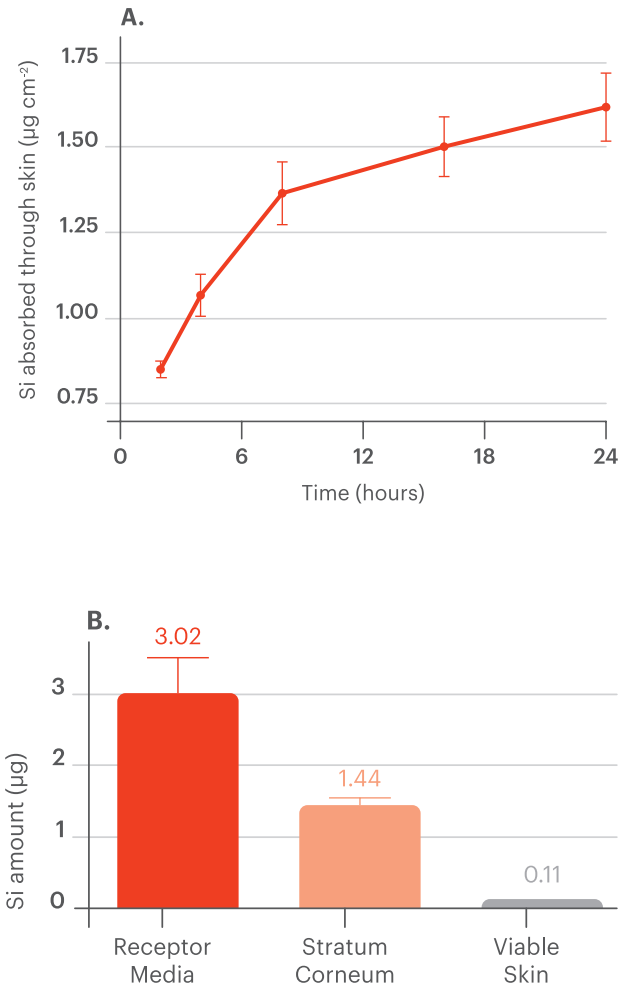


Figure 11. Permeation of monomethylsilanetriol in excised human skin.[115]
A. Permeation profile through 24 hours.
B. Levels of silicon detected after the expirement.

4.3 Metformin

Metformin hydrochloride (HCl) is a traditional, U.S. Food and Drug Administration (FDA)-approved drug which is currently used as a first-line drug of choice to treat type 2 diabetes. Nevertheless, it has been gaining momentum in clinical trials to target age-related processes.[118–120]

A clinical study conducted with over 100,000 patients identified that individuals having type 2 diabetes and being treated with metformin HCl, presented a longer life expectancy compared to nondiabetic patients used as control, and an even higher life expectancy compared to diabetic patients treated with other anti-diabetes drug.[121] The possible mechanisms of action of metformin as anti-aging can be seen in Figure 12.

Some of the key mechanisms of action include:

- Decreasing insulin levels and IGF-1 signaling[122]
- Inhibition of mTOR[123,124] and of mitochondrial complex 1 in the electron transport chain, coupled with reduction of reactive oxygen species (ROS) generation[125]
- Activation of AMP-activated kinase (AMPK)[126]
- Decrease in inflammation,[127] autophagy,[128] and cellular senescence[129]
- Reduction in DNA damage[130]

In addition, the effect on the AMPK that metformin presents can also play a potential role in weight loss, as can be seen in Figure 13. Metformin can also reduce the glycemic index, promoting the reduction of food intake, an important key to reduce weight.

It also promotes changes in hypothalamic-pituitary axis physiology, including sensitivity to leptin and insulin, as well as regulating oxidation and deposition of fat in the liver, skeletal muscle, and adipose tissue.[131,132]

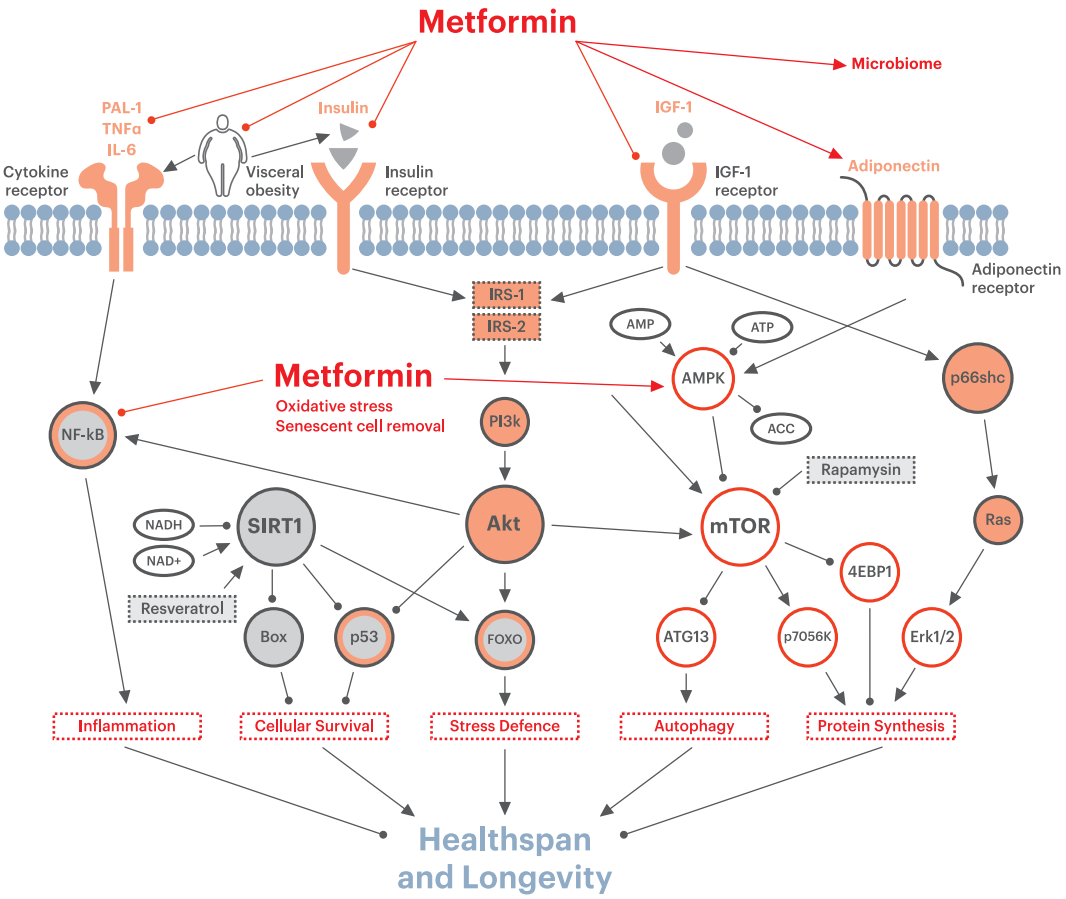


Figure 12. Molecular effects of metformin and their impact on healthspan and longevity..[118]

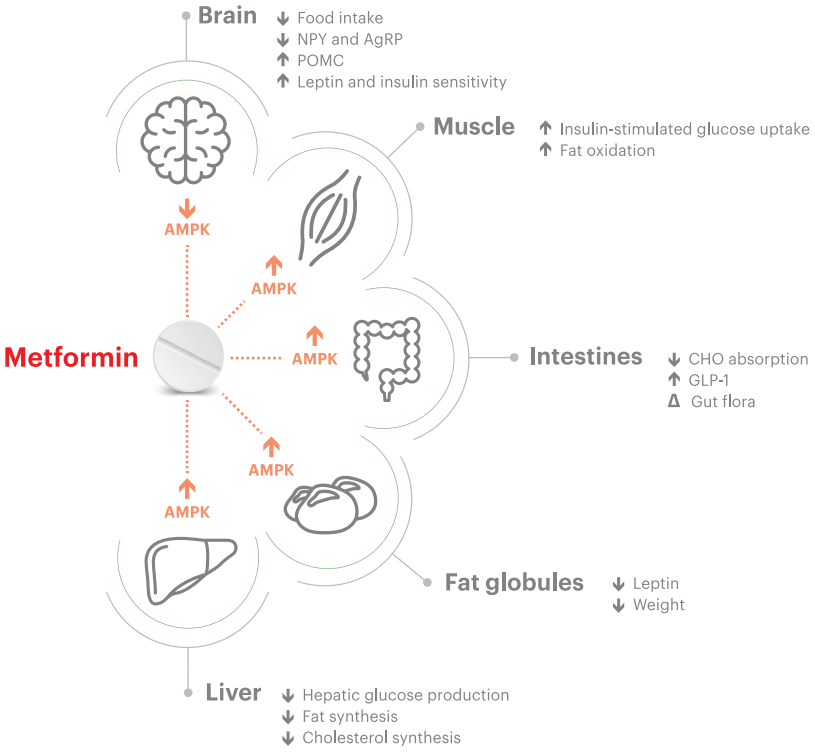


Figure 13. Effects of metformin on multiple body sites.[132]

Despite these possible clinical benefits, oral metformin HCl has some drawbacks, including a high incidence of gastrointestinal side-effects, rapid first-pass metabolism, patient non-compliance, possible hypoglycemia, low intestinal bioavailability and the he absence of a rate-controlled delivery.[133,134] All these factors can result in suboptimal results, reason why new pharmaceutical technologies have been evaluated for this API.[133,135–137] One of these new possibilities evaluated for metformin HCl was the transdermal route, using Pentravan® as vehicle in the permeation study discussed below.[138]

- **Study**

Transdermal Delivery of Metformin Hydrochloride from a Semisolid Vehicle.
International Journal of Pharmaceutical Compounding. Vol. 23 No. 1, p. 65-69, 2019.[138]

In the study, the steady-state metformin flux of metformin hydrochloride through the skin from the transdermal cream was found to be 3.91 µg/cm²/h, with a lag time of 0.51 h (Figure 14). The percentage permeated was 46.7%, very close to the oral bioavailability (which is around 50%)[118] - an equivalence to 93.4% of the oral dosage, possibly avoiding the side-effects commonly seen in patients.

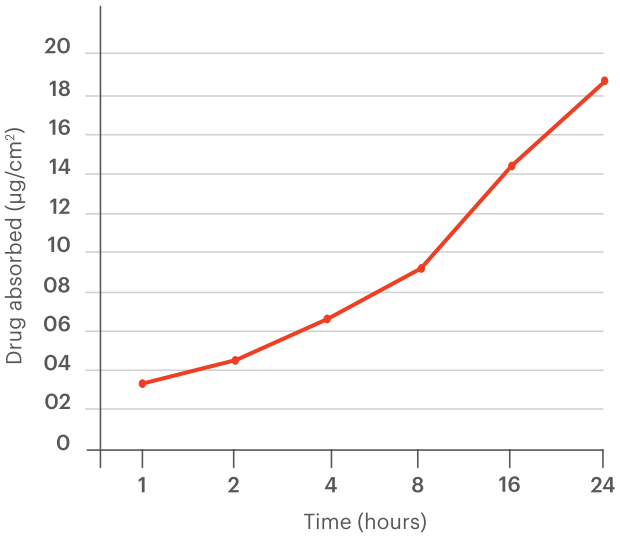


Figure 14. Permeation mean profiles (*n*= 6) of Metformin in Pentravan® transdermal vehicle, investigated using abdominal human excised skin.[138]

The study indicates the potential of delivering metformin hydrochloride through the transdermal route for anti-aging, anti-obesity, or other clinical indications, without the side effects of oral delivery.

4.4 Desmopressin

Desmopressin is a synthetic analog of vasopressin, but presents enhanced antidiuretic potency, decreased pressor activity, and extended half-life and duration of action compared to the natural hormone.[139] Its clinical applications include nocturia, nocturnal enuresis, central diabetes insipidus and bleeding disorders such as von Willebrand disease.[140] It is commonly administered orally, but it has low bioavailability, requiring high doses that can induce the onset of adverse effects, such as hyponatremia, which occurs in 4.9% of patients using desmopressin tablets.[141,142] Nocturia has a high prevalence in the elderly population, mostly in men.[143] It can be defined as the necessity to wake up during the night to empty the bladder, interrupting the sleep.[144] It can be associated with daytime fatigue and reduced quality of life, reason why its treatment is important during the aging process.[145]

To overcome the limitations of the oral route, transdermal administration of desmopressin could be used as an alternative to increase bioavailability and adherence.[146]

- **Study**

Transdermal desmopressin as an alternative dosage form for the treatment of nocturia.
Journal of Multidisciplinary Engineering Science and Technology.
Vol. 6, n. 10, p. 10888-10892, 2019.[147]

In this study, the permeation percentage obtained from the applied dose (400 µg) was 21.5% (86.5 µg). In comparison, desmopressin injections usually range from 1 to 20 µg, and the oral dose of 0.1 mg has an bioavailability ranging from 0.08% to 0.16%.[148] This is equivalent to at least an 134-fold increase and would account for a (much) greater bioavailability of desmopressin from transdermal Pentravan® compared to oral administration.

5. GYNECOLOGY

Vaginal delivery of drugs is an important route for poorly-absorbed and rapidly metabolized oral drugs,[149,150] as the region has a large surface area, a rich blood supply, and the avoidance of the first-pass hepatic metabolism.[151] Although some limitations of this delivery route (cultural background, personal hygiene, and cyclic physiological conditions),[152] it has been increasingly gaining attention for local or systemic conditions.

All ingredients in Pentravan® are safe for intravaginal use. Studies were conducted to evaluate and determine its benefits in gynecology.

5.1 Resveratrol

- **Study**

Permeation profiles of resveratrol cream delivered through porcine vaginal mucosa: Evaluation of different HPLC stationary phases.
Journal of Chromatography B.
Vol. 1002, n. 8-12, 2015.[153]

Resveratrol has important antioxidant and anti-inflammatory effects that could account for a possible vaginal route to treat conditions in which their actions could be beneficial – such as inflammatory process on the mucosa or underlying tissues. The objective of this study was to evaluate 20 mg/g of resveratrol in Pentravan®, through *in vitro* permeation experiments.

Different to its topical use, this study indicated that the vaginal mucosa forms a significant barrier acting against the transport of resveratrol in this formulation compounded with Pentravan®. The maximum flux obtained was 1.17 µg/cm²/h with a lag time of 0.23h (Figure 15).

From the study it can be seen that most of the API was retained within the vaginal mucosa instead of reaching the blood stream (Figure 16). Therefore, the API would be used for clinical conditions where the action on the mucosa is desirable, rather than for systemic use.

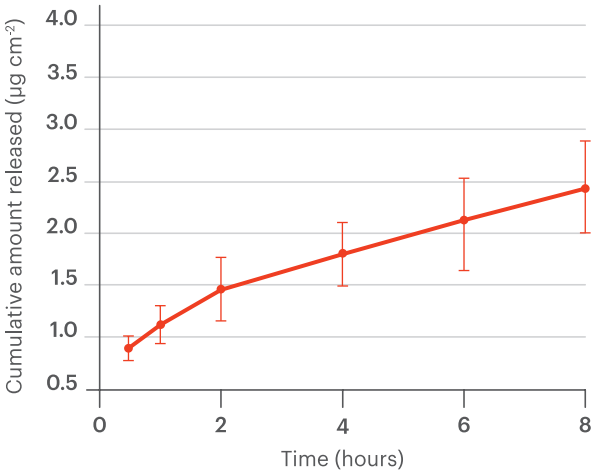


Figure 15. Permeation profiles of resveratrol vaginal cream using different stationery phases for separation/quantification. Values represent mean ± standard deviation (*n*= 6).[153]

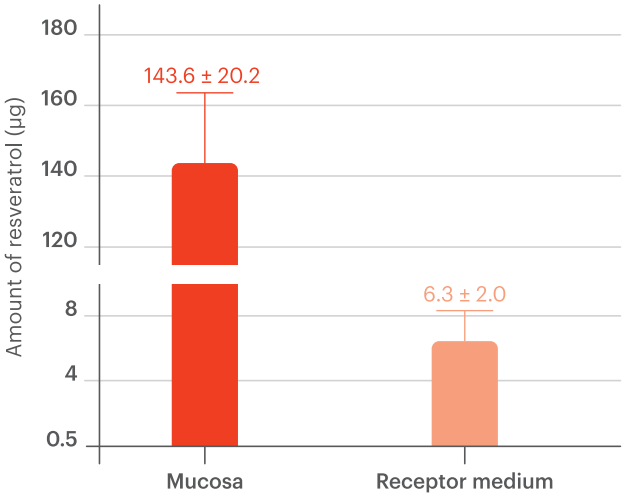


Figure 16. Mass balance of resveratrol permeation study from vaginal cream. Values represent mean ± standard deviation (*n*=6).

5.2 Gestrinone, dienogest, nimesulide and piroxicam

- **Study**

Feasibility Study Evaluating Pentravan® for the Intravaginal Administration of Active Pharmaceutical Ingredients to Reduce Pelvic Pain Related to Endometriosis.
Drug Delivery Letters. Vol. 8, p. 200-208, 2008.[154]

The objective of this study was to determine the permeation profile for vaginal creams containing dienogest (2.0 mg/g), gestrinone (5.0 mg/g), nimesulide (20 mg/g) or piroxicam (20 mg/g), compounded using Pentravan® as the transdermal vehicle. The APIs can play a role in pelvic pain related to endometriosis, due to their biological activity. Permeation percentages obtained differed widely with: 76.8% for dienogest, 46.9% for gestrinone, 1.1% for nimesulide and 12.7% for piroxicam.

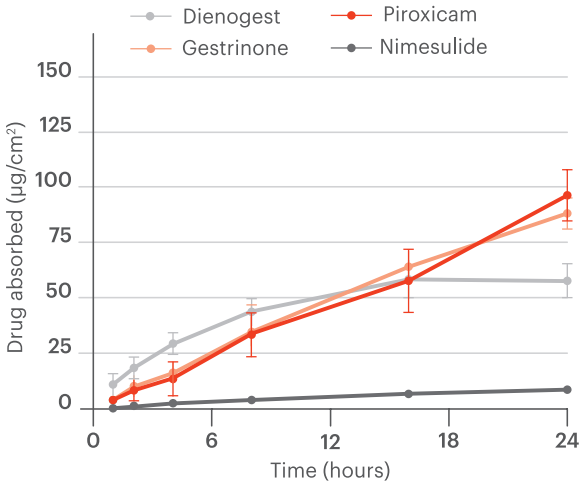


Figure 17. Permeation mean profiles (*n*= 6) of dienogest, gestrinone, nimesulide and piroxicam in Pentravan® transdermal vehicle, investigated using porcine vaginal musoca.[154]

Calculated fluxes (in µg/cm²/h) were: 15.98 for dienogest, 3.72 for gestrinone, 2.26 for nimesulide and 3.91 for piroxicam. Based on the plasma levels that these drugs need to achieve to obtain a clinical effect, a so called "flux to attempt" (in µg/cm²/h) was also calculated. These were 0.87 for dienogest, 0.69 for gestrinone, 70.45 for nimesulide and 9.64 for piroxicam respectively. Gestrinone and nimesulide presented adequate fluxes compatible with systemic absorption and clinic effect, while nimesulide and piroxicam would not be sufficiently absorbed, exerting their effects primarily locally on the mucosa surface - which is indicated for inflammatory processess in the region.

5.3 Progesterone and testosterone

- **Study**

Ex Vivo Evaluation of Intravaginal Progesterone and Testosterone to Treat the Luteal-phase Deficiency and Vaginal Atrophy.
International Journal of Pharmaceutical Compounding. Vol. 23, n. 1, p. 77-81, 2019.[155]

Vaginal atrophy is a common clinical finding that can affect the quality of life of women. The main symptoms include genital dryness, burning, and irritation; sexual symptoms of diminished lubrication and pain; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections.[156] Vaginal applied testosterone can improve the vaginal trophism.[157]

Lutheal phase support (LPS) is routinely used in assisted reproductive technologies, as progesterone deficiency is a hormone imbalance that could lead to luteal-phase deficiency and impact on the success of implantation rates.[158] The objective purpose of this study was to evaluate the transmucosal permeation of progesterone (50 mg/g) and testosterone (3.0 mg/g) using Pentravan® as vehicle for vaginal delivery. The percentage of the permeated drug, the drug flux and the lag times were, respectively, 0.4%, 1.19 µg/cm^{-2}/h and 1.8 h for progesterone, and 20.3%, 6.09 µg/cm^{-2}/h and 1.14 h for testosterone.

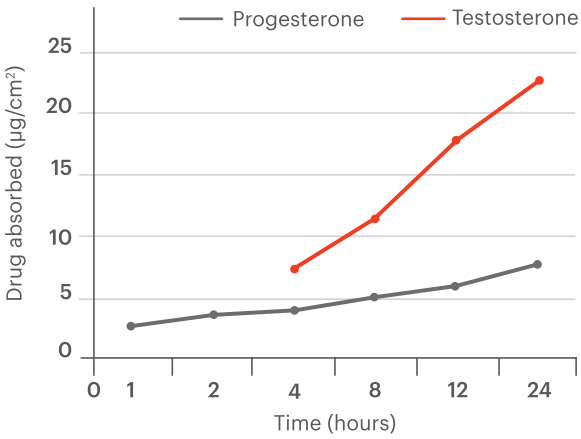


Figure 18. Vaginal permeation profiles of Progesterone and Testosterone.[155]

The permeation studies revealed that testosterone formulated with Pentravan® is potentially effective in both reaching the bloodstream and acting locally, as progesterone was mostly retained in the mucosa. The result is that this formulation is a promising drug intended for both local and systemic drug delivery when formulated with Pentravan®.

5.4 Clinical studies

• **Study**
Pulsatile administration of testosterone by the vaginal route using Pentravan®.
Proceeding from the 17th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI). p. 181-184, 2012.[159]

In this clinical study, testosterone 3 mg/g in Pentravan® was administered in the vulval/vaginal region to patients with low serum levels of testosterone and presenting symptoms of androgen deficiency. The treatment increased blood levels of testosterone in a pulsatile manner from 20 ± 15 ng/dl (n=26) to 312 ± 264 ng/dl (n=13) after 3 hours, followed by a rapid fall to 67 ± 40 ng/dl and 26 ± 10 ng/dl 12 and 24 hours, respectively, after application. An improvement in sexuality and the sensation of well-being was reported by 88% of the patients, with very few side effects. There was also a positive effect on vaginal atrophy.

• **Study**
Effect of vaginal gestrinone in Pentravan® on endometriosis patients using Mirena®: A preliminary report.
Clinical Obstetrics, Gynecology and Reproductive Medicine. Vol. 2, n. 2, p. 157-160, 2016.[160]

In this clinical study, the objective was to investigate the effect of low doses of vaginal gestrinone with oral *Pinus pinaster* extract and resveratrol on endometriosis-related pain in patients with deep endometriosis using Mirena® and still experiencing symptoms during use of this levonorgestrel-releasing intrauterine system.

In Group A (patients using Mirena® and further treated with a combination of 2.5 mg/g vaginal gestrinone in Pentravan® twice a week, together with 100 mg of oral *Pinus pinaster* extract and 30 mg of resveratrol daily, after 3-6 months of Mirena® starting dose; n=14), the use of Mirena® alone resulted in a small but significant decrease in pain scores. However, these patients were still experiencing breakthrough bleeding and pelvic pain. The introduction of the add-on treatment led to a further decrease in pain score, rendering these patients pain-free by the end of the second month of this combination treatment.

In Group B (same treatments, but starting together with Mirena®; n=6), pain scores similar to those found in Group A were achieved after the first treatment month.

The study concluded that the concomitant use of Mirena® with low doses of vaginal gestrinone in Pentravan®, in combination with oral antioxidants, is an effective treatment for deep endometriosis-related pain.

• **Study**
Treatment of Endometriosis and Leiomyoma with the Association of Miodesin and Gestrinone in Pentravan Through the Vaginal Route.
Journal of Clinical Review & Case Reports. Vol. 3, n. 7, p. 1-5, 2018.[161]

In this clinical study, the effects of Miodesin™ standalone or in association with gestrinone on uterine volume and pain scores were investigated in a group of patients with leiomyoma and endometriosis. Forty two patients with uterine leiomyoma and endometriosis were divided into 3 groups: Group A (n=16) was treated with vaginal gestrinone (5 mg/g, twice a week); Group B (n=16) was treated with vaginal gestrinone (2.5 mg/g, twice a week) and Miodesin™ (500 mg, daily); Group C (n=10) was treated with Miodesin™ (500 mg, daily). All medicines were dispensed vaginally using Pentravan® as vehicle.

The average uterine sizes before treatment were 200 cm^3, 334 cm^3 and 242 cm^3 (Groups A, B and C, respectively); after two months of treatment, a significant reduction in uterine volume was observed in all treated groups (but greater in group B). The proliferation rates in both stroma and endometrial gland were low, with a mean value of 2% with no significant differences between groups A and B. The treatment with gestrinone decreased total pain scores significantly when used either alone or in combination with Miodesin™ (the decrease was greatest in Group B).

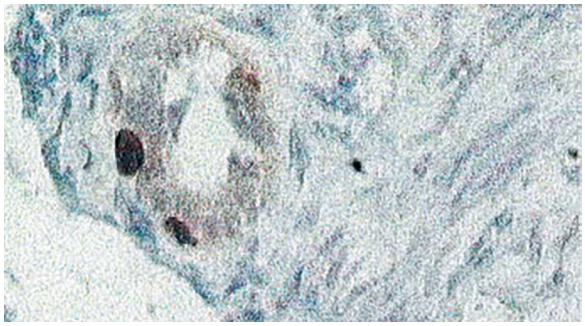


Figure 19. Basal endometrium in a patient using vaginal Gestrinone with Miodesin™ for 2 months. Note the low proliferation rates measured by Ki-67 in the glandular epithelium and stroma.[161]

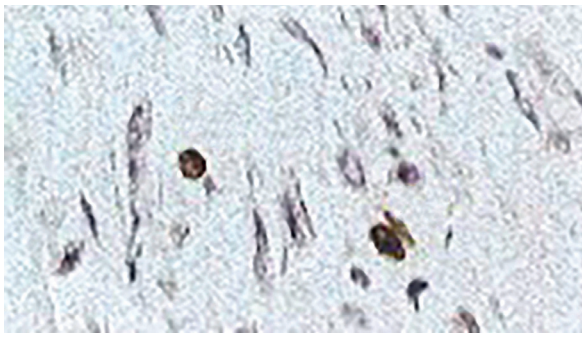


Figure 20. Low proliferation rates (Ki-67) in a leiomyoma of a patient using vaginal Miodesin™.[161]

The study concluded that Miodesin™ treatment increased the efficacy of gestrinone to reduce pelvic pain and uterine volume in patients with endometriosis and leiomyoma.

- **Study**

The Effects of Vaginal Gestrinone with Histone Deacetylase Inhibitors on Endometriosis-Related Pain and Endometrial Proliferation - A Short Study.
Journal of Clinical Case Studies
Vol. 3, p. 1-4, 2017.[162]

In this study, the objective was to investigate the effects of valproic acid or resveratrol (histone deacetylases inhibitors, or HDAC inhibitors), together with vitamin D3 in Pentravan® administered vaginally, on deep endometriosis-associated pain in patients undergoing treatment with gestrinone. Thirty patients with deep endometriosis and pelvic pain unresponsive to previous progestin-based treatment were divided into three groups: Group I (n=16) was treated for 6 months with vaginal gestrinone (GTN) (5 mg/g), twice weekly, and with oral pycnogenol (100 mg) and silymarin (400 mg), once a day; Group II (n=8) received the same treatment and also vaginal resveratrol (100 mg/g) and vitamin D3 (5000 U/g), administered daily; Group III (n=9) was treated with gestrinone together vaginal valproic acid (250 mg/g), daily. All vaginal formulations were prepared with Pentravan®.

There was a significant decrease in the mean pain score of patients in Group I from 9 at baseline to 3 after the first month of treatment. In Groups II and III, on the other hand, the pain score decreased from a mean of 9 to 1, a significantly greater decrease than that achieved in Group I (p=0.01). By the third month of treatment, all patients in all three groups were amenorrhoeic and pain-free, with no difference between the groups.

After the first treatment month, aromatase expression remained positive in the endometrium of 8/10 women (80%) in Group I compared to only 1/8 (12%) in Group II and 2/3 (66%) in Group III.

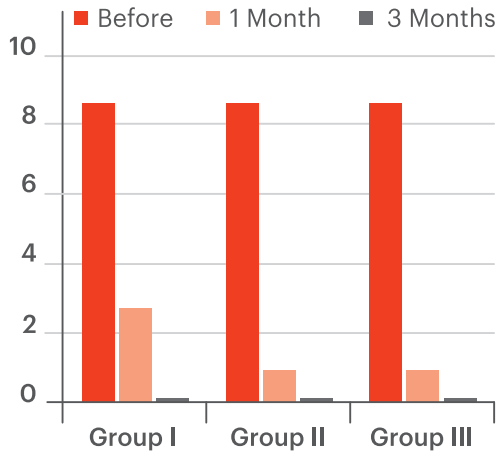


Figure 21. Reduction in pain scores following vaginal gestrinone either alone (Group I) or associated with vitamin D_3 and Resveratrol (Group II) or Valpoic acid (Group III).[162]
Group I x Group II-*P= 0.01*
Group I x Group II-*p= 0.01*

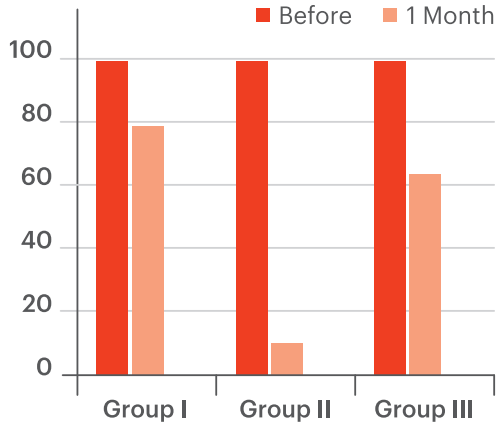


Figure 22. Effect of vaginal vitamin D_3 + Resveratrol or Valproic acid in Pentravan® on aromatase expression in endometriosis patients using vaginal gestrinone.[162]
Group I x Group II-*p= 0.006*
Group II x Group III-*p= 0.04*

The study concluded that the use of HDAC inhibitors in Pentravan® potentiated the pain-relieving effects of gestrinone in patients with deep endometriosis in the first month of treatment; however, this difference disappeared in the subsequent months. This suggests that if much faster pain relief were desired in cases of deep endometriosis, a combination of vaginal gestrinone with an HDAC inhibitor would be preferable.

6. COMPOUNDING WITH PENTRAVAN® AND PENTRAVAN® PLUS

API selection

Not all APIs are suitable for transdermal delivery, as permeation can be affected by the physicochemical nature of the molecule. **Table 1** summarizes the main characteristics that should be taken into account when compounding transdermal products.

Parameter	Characteristic
Lipophilicity	1 < logP < 3 (ideally, < 2.5)
Molecular size	< 600 Da
Melting point	< 200 °C
Daily dose	< 100 mg
Ionization (pKa x pH)	Non ionized

Table 1. Ideal API characteristics for transdermal delivery.

Therapeuticals classes to not compound in Pentravan®

- *Antibiotics:* the molecules are usually too large to pass completely through the skin. The risk of resistance to the antibiotic is significant.
- *Antipsychotics:* in most cases the molecule is too large to pass the skin completely and reach the bloodstream. In addition, good therapy with these drugs requires steady-state blood level maintenance of the drug.

Compounding process

The following general procedure can be used:
1. Calculate the quantity of each ingredient required for the total amount to be prepared.
2. Accurately weigh each ingredient.
3. Reduce all powder(s) to uniform, fine consistency, using the mortar and pestle.
4. Levigate the powder(s) with an appropriate amount of solvent to form a smooth paste mixing well. Transcutol® P can be used, due to its levigating and permeation enhancement properties.
5. Geometrically, add sufficient Pentravan® to final weight and mix well.
6. Package and label.
7. Store at room temperature (15-25 ˚C) away from excessive heat, unless specified otherwise for a given API.

Ideally, an ointment mill should be used between steps 5 and 6. This process helps to incorporate of the API in the cream, to reduce particle size and create a more uniform, elegant product.

An example of a suitable ointment mill is the FagronLab™ TRM Ointment Mill. A table-top adjustable three roller/ointment mill that reduces particle size in ointments, creams, pastes, gels, and suspensions for pharmaceutical compounding or other applications.

Smaller and more uniform particles mean more active ingredient surface area, maximizing the treatment benefits. The three rollers rotate in opposite directions and at different speeds, creating a shear force that moves the compound through the mill.

For emulsions, it also helps in the stabilization of the micelles, as smaller micelles have less tendency to aggregate. In this sense, problems such as creaming, sedimentation, flocculation, coalescence, and phase separation are avoided.

- **Study**

Towards the Importance of a Roller Mill in Compounding Practice: An Experimental Approach.
International Journal of Pharmaceutical Compounding. Vol. 23, n. 2, p. 154-156, 019.[163]

The objective of this study was to standardize and validate the use of an ointment rill (roller mill) through the evaluation of particle size and content uniformity (CU). Particle size was evaluated in a cream using Pentravan® as the vehicle and containing testosterone 10 mg/g or a gel of benzoyl peroxide 5%.

Each formulation was passed three times through the roller mill. The use of a roller mill decreased the average particle size measured by dynamic light scattering (DLS) in both tested preparations. It also decreased the polydispersity index (PDI), which is a measure of the broadness of the distribution size (a higher value indicates that the material is more polydispersed). In this sense, the roller mill was able to narrow the range of particle size within the preparations, making them more homogeneous.

Results of dynamic light scattering measurements (particle size) of products compounded using a roller mill.

Product	Average diameter (nm)	Polidispersity index
Benzoyl peroxide 5% gel (not passed through the roller mill)	2.990	7.36
Benzoyl peroxide 5% gel (passed through the roller mill)	1.580	0.66
Testosterone 1% in Pentravan® (not passed through the roller mill)	3.544	9.36
Testosterone 1% in Pentravan® (passed through the roller mill)	1.840	0.72

Results are given as mean of three determinations.

Table 2. Results of dynamic light scattering measurements (particle size) of products compounded using a roller mill.[163]

Scanning electron microscopy (SEM) images confirm the decrease in particle size shown in the DLS analyses. The particles are not only smaller but also more homogeneous, when compared to the sample not passed through the roller mill.

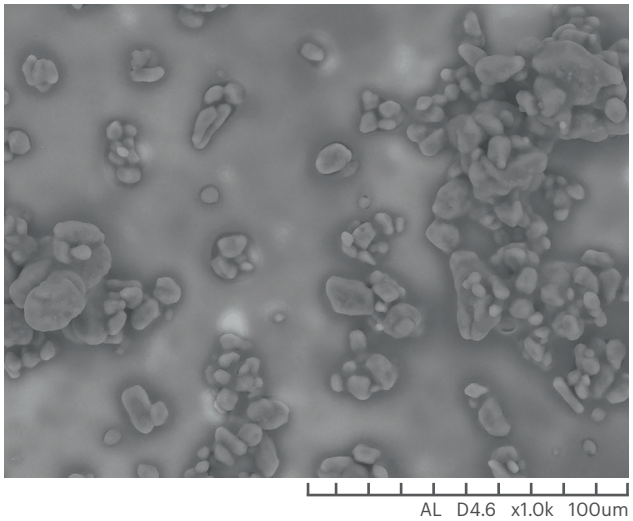


Image 1. The preperation **before** it was passed through the roller mill.[163]

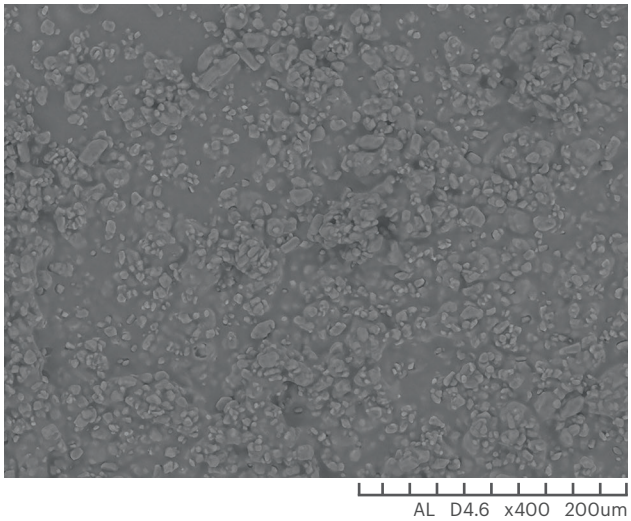


Image 2. The same preperation **after** it was passed through the roller mill.[163]

As for content uniformity, the formulations that were ground in the roller mill were more uniform with respect to their active. These results indicate that the roller mill played an important role in the emulsion compound preparation process.

Content uniformity of the products compounded for the study

Sample	Progesterone 50 mg/g		Estradiol 1 mg/g (in Biest)		Estriol 4 mg/g (in Biest)	
	Not passed in roller mill	Passed in roller mill	Not passed in roller mill	Passed in roller mill	Not passed in roller mill	Passed in roller mill
1	88.94	90.55	120.00	95.65	80.24	91.09
2	88.26	88.68	74.00	91.46	99.23	91.28
3	86.19	88.54	99.484	99.44	100.42	98.50
4	83.31	91.49	101.75	94.27	85.25	93.45
5	80.34	95.81	86.56	95.52	111.89	94.35
6	90.70	96.00	112.28	98.12	100.21	95.44
7	88.27	94.22	101.67	97.23	117.25	95.62
8	84.11	94.76	94.70	99.25	92.44	97.10
9	80.73	96.98	96.70	93.32	97.42	89.85
10	89.47	88.14	95.29	91.12	94.93	92.99
Average	86.03	92.52	98.24	95.54	98.05	93.97
Standard deviation	3.71	3.42	12.67	3.00	10.91	2.77
Acceptance value	21.36	14.20	30.66	10.17	26.63	11.8

Note: Acceptance value should be lower than 15.0.

Table 3. Content uniformity of the products compounded for this study.[163]

The conclusion of the study was that the roller mill used does, in fact, play a role in the final aspect and quality of pharmaceutical semisolid dosage forms, whether reducing particle size or improving homogenization.

Packing

Choosing the right packing is essential for the quality of the transdermal product, as it helps to deliver the right amount for the patient during use. Delivered-Dose Uniformity in Metered Dose Containers is a requirement from the *United States Pharmacopeia* <3> Topical and transdermal drug products—product quality tests.[164] Metered-dose containers, such as airless pump containers, are the most adequate to always deliver the right dose.

• Study

Evaluation of Percutaneous Absorption Performance for Human Female Sexual Steroids into Pentravan Cream. **International Journal of Pharmaceutical Compounding. Vol. 18, n. 4, p. 332-340, 2014.**[98]

This study also evaluated the influence of the packing on the final product. Two packages (1 and 2) were evaluated, from different manufacturers.

Results from the optimization of the semisolid dosage form preperation.

Sample (mL, n=3, genuine replicate)	Ground (d=0.922778)	
	Packaging 1	Packaging 2
1	0.994	0.914
2	1.009	0.993
3	1.013	1.037
4	1.005	1.000
5	0.986	0.947
6	1.064	0.958
Mean	1.012	0.975
Standard deviation	0.027	0.043
Coefficient of variation (%)	2.701	4.436

Table 4. Results from the optimization of the semisolid dosage form.[98]

The results show that Packing 1 delivers more consistent doses than Packing 2. Therefore, it is essential to check with the suppliers of metered-dose packings if the quality checks and calibration have been performed. The adequate tests for such purpose can be found at Delivered-Dose Uniformity in Metered Dose Containers.[165]

Dispensing

Labeling the product and giving full information on the correct use of the product is another key factor for the therapeutic success. The following instructions should be included:

- Press the dispenser of the packing until the end, to obtain the full dose.
- Apply with pressure over the chosen body area.
- Deplete all the product in your hand, the maximum possible. Spread it well.
- Wait 30 min until wear clothes in the region applied and to have physical contact with people.

Figure 23 highlights the best body sites for application of transdermal products: abdomen, back, arms (inner part), and thighs (inner part). It is best to avoid hairy regions, as hair can influence on the permeation profile of the drug. It is also advisable to alternate application sites, to not saturate the same area with product.[166,167]

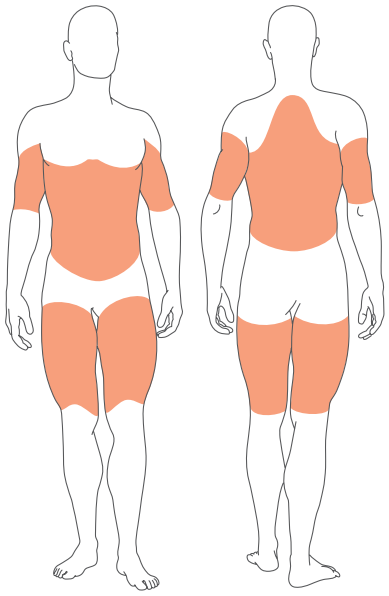
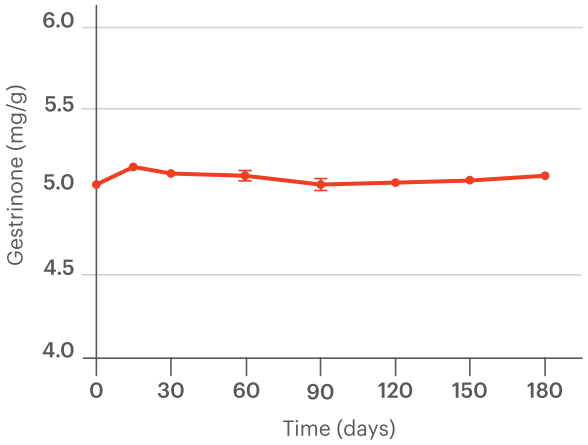
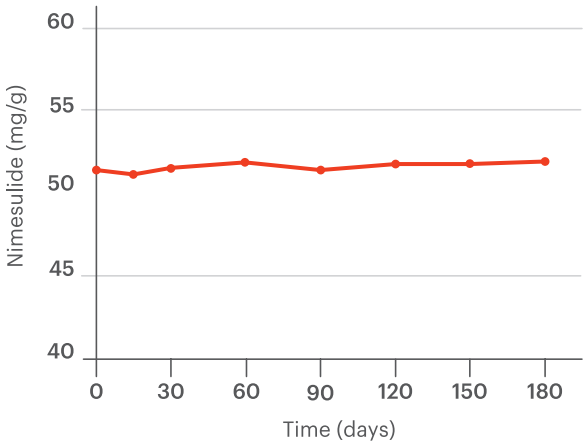


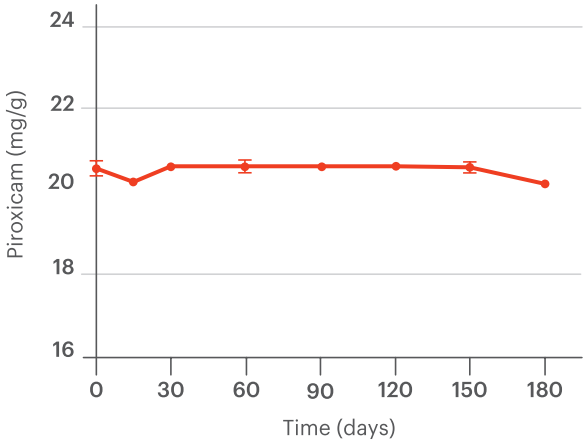
Figure 23. Most adequate sites to apply Pentravan® products, in order to obtain the maximum absorption.

Stability

Studies conducted with gestrinone 5.0 mg/g, nimesulide 50 mg/g and piroxicam 20 mg/g showed that the BUD of such products are 180 days, indicating a high stability of Pentravan® and compatibility with APIs.[168] In the absence of stability information that is applicable to a specific drug or preparation, the United States Pharmacopeia general chapter <795> (Pharmaceutical compounding—nonsterile preparations) could be used. As instructed in this chapter, "for water-containing topical/dermal and mucosal liquid and semisolid formulations—The BUD <Beyond-Use-Date> is not later than 30 days".[169] The BUD shall not be later than the expiration date on the container of any component.







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