PENTRAVAN: SCIENTIFICALLY PROVEN EFFICACY AND SAFETY

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Introduction

Transdermal drug delivery has contributed significantly to medical practice. The transdermal route represents an attractive alternative to the oral route and also provides an alternative option to hypodermic injections (PRAUSNITZ; LANGER, 2008).

Transdermal delivery has a variety of advantages compared to the oral route. It could be a means to avoid or minimize adverse effects resulting from the oral ingestion of drugs. As observed with transdermal estradiol systems, and in contrast to the oral formulation of this hormone, there are no occurrences of liver damage (CRAMER; SAKS, 1994). Transdermal pharmaceutical forms have now often been considered as a means to overcome limitations of other routes of drug delivery. In the pharmacotherapy context, the main advantages of the transdermal route are the absence of intestinal metabolism and the first pass effect of the liver; promoting the slow absorption of the active pharmaceutical ingredient, reducing the plasma concentration levels of the active pharmaceutical ingredients with preserved stable and controlled blood levels for an extended period of time; decreased metabolic effects, including gastrointestinal and systemic adverse effects; improvement of *patient compliance* through the convenience of decreased delivery frequency and non-invasive, painless and easy administration (PRAUSNITZ; LANGER, 2008; KOPPER; GUDEMAN; THOMPSON, 2008; SONI; KUMAR; GUPTA , 2009, GUY, 2010, SHINGADE et al., 2012, SHARMA, SANI, RAMA, 2013).

Pentravan® cream was named after its extended meaning in English, i.e**. *Pen*e*tra*tion *enhanced ***van****ishing cream*, and its formulation was developed by the Fagron Group. It consists of a transdermal vehicle of great interest and application in the context of compounding pharmacy and has a safe composition and high level of scientific laboratory evidence proving its efficiency in enhancing skin permeation for several active pharmaceutical ingredients. Clinical studies also demonstrate its efficacy and acceptability in transmucosal vulvovaginal drug delivery. Pentravan® has been prescribed globally by professional healthcare providers as a percutaneous base in several individualized formulations prepared by pharmacies and used by numerous patients in several countries.

Pentravan® Composition - Description and Safety

Pentravan® is an oil-in-water vanishing base emulsion with a polymer matrix and a liposomal matrix. Its formulation also comprises a variety of permeation enhancers used to ensure and provide the transdermal release of active ingredients (BOURDON et al., 2016). It is a fragrance-free or perfume-free formulation, with no parabens, petrolates and 1.4-dioxane residues and any other potentially toxic residues or which may act as hormone or xenoestrogen disruptors. Its composition includes GRAS (*Generally Recognized as Safe*) ingredients only and is approved by regulatory agencies around the world for pharmaceutical, food and/or cosmetic use. Inactive ingredients include fatty alcohols, fatty acids, esters, phospholipids, antioxidants, preservatives not derived from parahydroxybenzoates**, permeation and sensory enhancers, natural humectants, emulsifiers and buffering agents for pH adjustment. Phospholipids in the formulation come from phytoestrogen-free high-purity soy lecithin as listed in studies published by Thompson et al. (THOMPSON et al., 2006). Although phytoestrogens are present in soybeans, they are **not** found in soy lecithin and its phospholipids (THOMPSON et al., 2006; ANDERSON; COTTERCHIO; BOUCHER, 2011). The phospholipid matrix is biocompatible and partially responsible for the high permeating power of Pentravan® and several other transdermal vehicles and vectors, including liposomes.

Pentravan® Skin Permeation Mechanism and Efficacy

The transdermal permeation mechanism provided by Pentravan® involves the interruption of the phospholipid bilayer of the stratum corneum which facilitates transdermal drug delivery without damaging it. Its truly vanishing property and fast permeation leave no sticky residues on the skin, preventing the cream from transferring to clothing and ensuring greater therapeutic effectiveness. Therefore, a greater amount of the delivered drug will be available for a shorter period of time to establish the therapeutic effect. The promising permeation efficacy of the Pentravan® base has been evidenced by multiple laboratory and clinical studies, and several of them have been published in different and important indexed scientific publications. Pentravan® is indeed the transdermal vehicle of interest and

compounding application with the highest level of scientific evidence in the world, and it is prescribed by professional healthcare providers in several individualized formulations (e.g. hormone replacement therapy; treatment of chronic pain) prepared by pharmacies and used by patients from several countries. Table 1 shows the main studies on skin and vaginal mucosa permeation carried out in Franz cells up to the present moment, including some published and unpublished studies as well as some submitted for publication.

Table 1. Pentravan® Permeation Studies in Franz Cells

Active Ingredient	Conc. % w/w	Membrane	Stationary Permeate Flux (*Js*)	% Total Permeate (Relating to the Applied Dose)	Reference
Progesterone	5% (50mg/g)	Human skin (*ex vivo*)	4.55μg/cm^{2}h^{-1}	68.31% (24h) 76.80% (48h)	Polonini et al., 2014a
Progesterone	5% (50mg/g)	Porcine vaginal mucosa	1.19μg/cm^{2}h^{-1}	42.90% (24h)	Submitted for publication
Progesterone (new formula)	5% (50mg/g)	Human skin (*ex vivo*)	4.6μg/cm^{2}h^{-1}	73.20%(24h)	Unpublished
Testosterone	10% (100mg/g)	Human skin (*ex vivo*)	0.095±0.026μg/cm^{2}h^{-1}	ND	Lehman;Raney, 2012
Testosterone	1% (10mg/g)	Human skin (*ex vivo*)	8.77μg/cm^{2}h^{-1}	68.30% (24h)	Unpublished
Testosterone	0.3% (3mg/g)	Porcine vaginal mucosa	6.09μg/cm^{2}h^{-1}	44.07% (24h)	Submitted for publication
Testosterone (new formula)	1% (10mg/g)	Human skin (*ex vivo*)	ND	69.4%(24h)	Submitted for publication
Estradiol (E2)	0.1% (1mg/g)	Human skin (*ex vivo*)	1.15μg/cm^{2}h^{-1}	86.33%(24h) 99.9 (48h)	Polonini et al., 2014a
Estradiol(E2) (new formula)	0.1% (1mg/g)	Human skin (*ex vivo*)	ND	91.0%(24h)	Unpublished
BIEST (E2 + E3)	E2:0.1%(1mg/g) E3:0.4%(4mg/g)	Human skin (*ex vivo*)	E2=1.13μg/cm^{2}h^{-1} E3=0.27μg/cm^{2}h^{-1}	E2:73.53%(24h) 84.7%(48h) E3:43.67%(24h) 49.9% (48h)	Polonini et al., 2014
BIEST (E2 + E3) (new formula)	E2:0.1%(1mg/g) E3:0.4%(4mg/g)	Human skin (*ex vivo*)	E2=ND[1] E3=ND	E2:78.8%(24h) E3:48.50%(24h)	Unpublished
Oxandrolone	2% (20mg/g)	Human skin (*ex vivo*)	1.20μg/cm^{2}h^{-1}	25.9%(24h)	Polonini et al., 2016
Gestrinone	0.5% (5mg/g)	Porcine vaginal mucosa	3.72μg/cm^{2}h^{-1}	61.40%(24h)	Submitted for publication
Ketoprofen	10% (100mg/g)	Human skin (*ex vivo*)	1.627±0.422μg/cm^{2}h^{-1} (28h)	ND	Lehman;Raney, 2012
Ketoprofen (new formula)	10% (100mg/g)	Human skin (*ex vivo*)	3.82μg/cm^{2}h^{-1}	63.6%(24h)	Unpublished
Piroxicam (new formula)	0.5% (5mg/g)	Human skin (*ex vivo*)	ND	42.1%(24h)	Unpublished
Piroxicam	2.0%(20mg/g)	Porcine vaginal mucosa	3.91μg/cm^{2}h^{-1}	59.25%(24h)	Submitted for publication
Nimesulide (new formula)	2%(20mg/g)	Human skin (*ex vivo*)	ND	20.7%(24h)	Submitted for publication
Nimesulide	5% (50mg/g)	Porcine vaginal mucosa	2.26μg/cm^{2}h^{-1}	58.87%(24h)	Submitted for publication
Resveratrol	2%(20mg/g)	Human skin (*ex vivo*)	0.87μg/cm^{2}h^{-1}	62.6%(24h)	Polonini et al., 2014b
Resveratrol	2%(20mg/g)	Human skin (*ex vivo*)	.....	64.96%(24h)	Almeida et al., 2015
Resveratrol	2%(20mg/g)	Porcine vaginal mucosa	1.17μg/cm^{2}h^{-1}	86.6%(24h)	Polonini et al., 2015
Taxifolin (*Pinus Pinaster* Extract Marker) (new formula)	0.5% (5mg/g)	Porcine vaginal mucosa	74.89μg/cm^{2}h^{-1}	89.22%(24h)	Submitted for publication
Ondansetron	1.6%	Pig Ear Skin	606μg/cm^{2}h^{-1} (7.5h)	.....	Bourdon et al., 2016

ND = Not Determined.

E2 = estradiol; E3 = estriol

Qcum = accumulated amount of drug released into the Franz cell recipient chambers.

Clinical Studies Conducted Using Active Pharmaceutical Ingredients Delivered on Pentravan®

The vaginal route has now been considered of great interest for drug delivery. It is appropriate for both local and systemic drug delivery. The vaginal route provides different advantages over the oral route. Its wide surface area is richly supplied with blood and highly permeable to a wide variety of substances of different molecular weights, thus avoiding liver first-pass metabolism and the occurrence of gastrointestinal adverse effects. The physiological characteristics of the vaginal route not only contribute to these pharmacokinetic advantages, but may also result in increased bioavailability for some drugs. However, drug absorption through the vagina may be affected by changes in epithelial thickness and changes in the vaginal medium that occur as a consequence of aging and cyclic physiological conditions or sexual intercourse. In addition, both the self-cleaning action of the vaginal tract and the leakage loss after applying the pharmaceutical form may also reduce the bioavailability of drugs administered by this route (MACHADO et al., 2015). Therefore, efficiency in promoting permeation and vaginal capacity of retaining the vehicle are desirable attributes to increase the degree of absorption of active pharmaceutical ingredients by vaginal route.

Pentravan® has been used as a vehicle for vaginal transmucosal release of active pharmaceutical ingredients, and its efficacy and suitability for this route of administration have been confirmed by successive clinical studies. Table 2 lists published and unpuplished studies using Pentravan® as a vaginal transmucosal vehicle.

Table 2. Published Clinical Studies Using Pentravan® as a Vaginal Transmucosal Vehicle

Active Pharmaceutical Ingredient Delivered	Delivered Dose	Route of Administration	N (No. of subjects)	Clinical Condition	Reference
Gestrinone 5mg/mL	5mg/day	Vaginal	47	Endometriosis	MAIA Jr.et al., 2015
Gestrinone 5mg/mL	5mg/day	Vaginal	15	Endometriosis	MAIA Jr et al., 2014a
Gestrinone 2.5m/mL	2.5mg/day	Vaginal	20	Endometriosis	MAIA Jr., 2016
Danazol 100mg/mL	100mg/day	Vaginal	14	Endometriosis	MAIA Jr.et al., 2014b
Testosterone 3mg/mL	3mg/day	Vulvar	26	Vaginal Atrophy	MAIA Jr.et al., 2013
Resveratrol 100mg/mL plus Vitamin D3 5000 IU/mL	100mg/day (resveratrol)plus 5000IU/day (vitamin D3)	Vaginal	33	Endometriosis	MAIA et al., 2016 (unpublished)
Valproic acid 250mg/mL plus gestrinone 5mg/mL	250mg/day (valproic acid) plus 5mg (gestrinone)	Vaginal	33	Endometriosis	MAIA et al., 2016 (unpublished)

Conclusion

Although Pentravan® polymer/liposomal matrices contain permeation-enhancing ingredients traditionally used in other semi-solid transdermal preparations, Pentravan® is distinguished by a higher absorption rate when compared to other bases available on the market. Evidence of its higher permeation enhancement as documented by successive laboratory and clinical studies provides greater prescriber, patient, and drug safety. In addition, its composition and practicality as a "*ready-to-use base*" in pharmaceutical compounding gives the pharmacist greater practicality and speed in preparing transdermal delivery systems with several active pharmaceutical ingredients. The reproducibility in the quality of formulations and therapeutic results add to the other Pentravan® attributes, making it a transdermal vehicle of choice for the compounding pharmacy.

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