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Chemical Enhancers for the Absorption of Substances Through the Skin: Laurocapram and Its Derivatives

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ABSTRACT Absorption enhancers are substances used for temporarily increasing a membrane's permeability (e.g., the skin and mucosa), either by interacting with its components (lipids or proteins) or by increasing the membrane/vehicle partition coefficient. This article presents the results of biophysical and permeability studies performed with Laurocapram and its analogues. As shown, Laurocapram and its analogues present different enhancing efficacies, for most of both hydrophilic and lipophilic substances. The enhancing effect of Laurocapram (Azone®) is attributed to different mechanisms, such as insertion of its dodecyl group into the intercellular lipidic bilayer, increase of the motion of the alkylic chains of lipids, and fluidization of the hydrophobic regions of the lamellate structure. Toxicological studies reveal a low toxicity for Laurocapram, and for some derivatives, a relationship exists between toxicity and the number of carbons in the alkylic chain. Very important, when applied to human skin, Laurocapram shows a minimal absorption, being quickly eliminated from circulation. However, although Laurocapram and its derivatives have been shown to provide enhancement, they have not been widely accepted because of their suspected pharmacological activity or questions about their safety.

KEYWORDS Absorption enhancers, Laurocapram, Permeation

INTRODUCTION

Over the last decades, there has been an increase in the use of chemical substances that are absorbed through the skin, either for local or general therapeutic purposes. In the pharmaceutical area, percutaneous administration has several advantages, but the most important is, unquestionably, the possibility of avoiding the first-pass effect. However, when a drug is formulated to be administered by this route, it is necessary to include excipients acting as absorption enhancers, due to the skin's natural resistance to the penetration of exogenous substances. The design, synthesis, and evaluation of these molecules is a primary field of interest in the chemicopharmaceutical area.

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An absorption enhancer is a substance that increases the partition and diffusion of active agents to and across the permeability barrier (Khaled et al., 2001); its action mechanisms may be summarized as follows: a) Increased fluidity of the membrane's lipidic bilayers, with the corresponding reduction of the vitreous transition temperature; b) extraction of intercellular lipids; c) interaction with proteic components; d) alteration of the enzymatic barrier; e) increase of the solute's thermodynamic activity; f) codiffusion of the enhancer and the solute; and g) increase of stratum corneum hydration. Table 1 summarizes a number of enhancers whose action mechanism is indicated according to the preceding points (Goffin et al., 2000; Ganem et al., 1998). Among absorption enhancers, Laurocapram has been one of the most effective for substances of both lipophilic and hydrophilic nature.

Considering the topic's modernness and the implications of new molecules as enhancers in the pharmaceutical chemistry field, the objective of this review is to gather together all the information on Laurocapram and its derivatives, describing its physicochemical characteristics, the proposals about its potential mechanism of action, the main results obtained when it is used as an enhancer, and the toxicity studies.

LAUROCAPRAM'S GENERAL CHARACTERISTICS

Laurocapram, whose chemical names are 1-dodecyl azacycloheptan-2-one, 1-dodecyl hexahydro-2H-azepin-2-one, *N*-dodecyl-3-caprolactam, and Azone® (AZO) as trade name, is shown in Fig. 1. Derived from caprolactam, it has uses as a percutaneous absorption enhancer and a physiological active agent, and has an intrinsic anti-inflammatory activity (Budavari et al., 1996; Allan, 1995). Fig. 2 shows the charge distribution of Laurocapram (Rosendo, 1999).

Laurocapram was proposed in 1976 as a penetration enhancer (Rajadhyaksha, 1976a–c, 1978). It has been widely studied since 1980 (Rajadhyaksha, 1982, 1983a–d, 1984a,b; Yang et al., 2001; Vaidyanathan et al., 2001; Xie, 1998; Ding & Zheng, 1997; Bymaster et al., 1996; Peck & Minaskanian, 1995; Petersen et al., 1994; Samour & Eisenberg, 1993; Sato et al., 1992; Potts & Francoeur, 1989; Minaskanian & Peck, 1998; Williams & Barry, 2004), and it is a clear, amber liquid, whose molecular mass is 281.49 Da, its melting point is –7°C, and its boiling point is 160°C at 0.05 mmHg. The octanol/water partition coefficient is 6.21 (Allan, 1995; Afouna et al., 2003); other authors report 6.6, showing it is a highly lipophilic material (Barry, 1987).

TABLE 1 **Skin Absorption Enhancers and Their Probable Mechanism of Action**

Enhancer	Examples	Probable mechanism of action[a]
A. Solvents		
1. Water		g
2. Alcohols	Methanol, Ethanol	a, b
3. Alkylmethyl sulfoxides	Dimethyl sulfoxide, dimethylformamide	b
4. Pirrolidones	2-Pirrolidone, *N*-methyl-2-pirrolidone	g
5. Laurocapram and derivatives		a
6. Other	Propylene glycol	f
B. Surfactants		
1. Anionic	Sodium dodecyl sulphate	a, b, c
2. Cationic	Cethyl trimethyl ammonium bromide	a, b, c
3. Nonionic	Tweens, Brijs, Poloxamers	a, b, c
4. Acids and fatty alcohols	Oleic acid, lauric acid	a
5. Bile salts	Calcium thioglycolate	a, b, c
C. Other		
1. Urea		g
2. Terpenes and essential oils	Menthol and limonene	a
3. Cyclodextrins		e
4. Enzymatic inhibitors		d

[a]Letters as indicated in the text.
Data modified from Ganem et al. (1998).

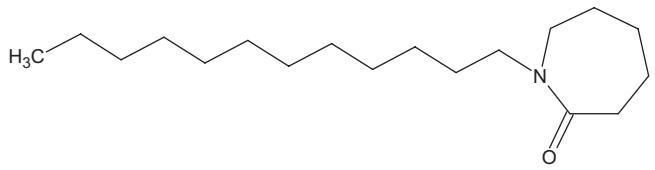

FIGURE 1 **Laurocapram's chemical structure.**

Laurocapram is miscible with most organic solvents, and it is an excellent solubilizer of a wide range of drugs; it is rapidly incorporated into different formulations, showing a high chemical stability, and is compatible with most excipients (Allan, 1995). Because Laurocapram contains a large alkylic chain, limited by a polar cycle called azacycloheptan-2-one (Naik & Guy, 1997), it is an effective enhancer for both hydrophilic and hydrophobic drugs of different molecular weights, such as steroids, antibiotics, and antivirals (Afouna et al., 2003), including also peptide molecules, such as insulin and vasopressin (Allan, 1995; Naik & Guy, 1997). Laurocapram is generally used at low concentrations, 1–5% (v/v), and its enhancer activity may be increased by using cosolvents, including propylene glycol (PG) (Wiechers, 1990a–c, 1995; Hadgraft, 1996).

However, although Laurocapram has been shown to be highly effective for a large number of substances, it cannot be considered a universal enhancer. Although there are many proposals regarding its mode of action and the way in which it interacts with the components of biological membranes, as described below, deeper studies are required on its interaction with other drugs and the influence of the vehicles or formulations used (Ganem-Quintanar et al, 1997).

The permeation process across a biological membrane cannot be viewed only as a diffusion phenomenon. The interactions that naturally occur between the lipids and proteins that constitute the membrane should be taken into account, as well as those that occur between the drug and the membrane, the formulation (including the enhancer) and the membrane, and the drug and the formulation's components. Therefore, it is evident that the physicochemical properties of the drug (e.g., molecular weight, pKa, solubility, and partition coefficient) and of the vehicles used (e.g., solubility parameter and dielectric constant) are factors that will affect the degree of promotion achieved with Laurocapram (Allan, 1995; Barry, 1987; Naik & Guy, 1997; Wiechers, 1990a–c, 1995; Hadgraft, 1996; Ganem-Quintanar et al., 1997; Michniak, 1995).

MECHANISM OF ACTION

In the last years, various mechanisms of action have been proposed for Laurocapram. However, all the studies follow the same guideline and are focused on showing that Laurocapram interacts with the stratum corneum (SC) lipids, causing their disruption and creating "hollows" between them, which facilitates the passage of substances. Thus, several authors, Allan (1995) among them, point out that Laurocapram interacts

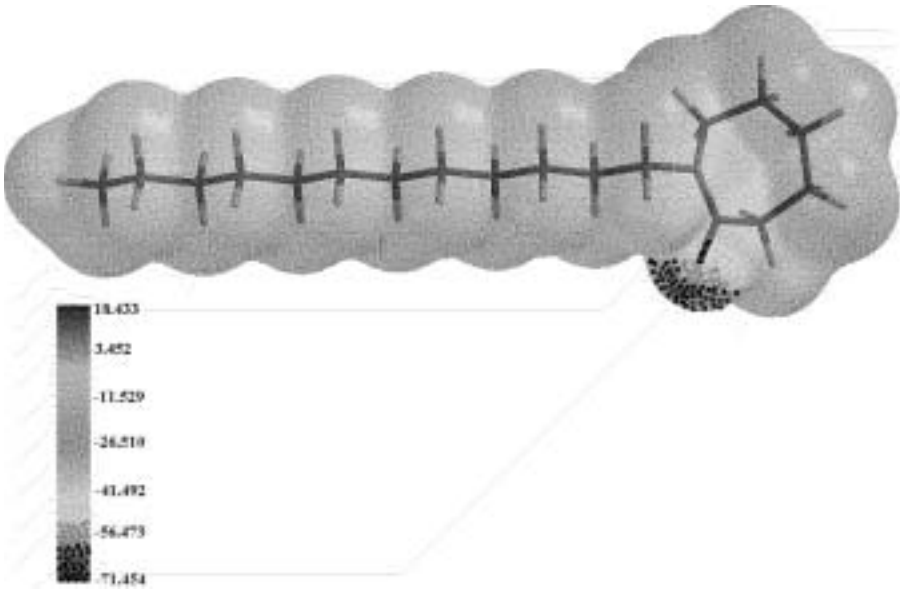

FIGURE 2 **Laurocapram´s electrical distribution loads; units in electronvolts (eV).**

with the intercellular lipids, fluidizing the hydrophobic regions of the lamellate structure and increasing the diffusion in the skin. Laurocapram has an alkylic chain of 12 carbons, which suggests the formation of hollows in the intercellular space, through the interruption of the ceramide-cholesterol or the cholesterol-cholesterol interactions.

Barry (1987) performed a study by differential scanning calorimetry (DSC), which reveals that the lipid structure is altered by the effect of Laurocapram. By DSC, it is observed that the SC presents four major transitions at the following temperatures: T_1 (30°C), T_2 (72°C), T_3 (85°C), and T_4 (102°C), which are shown in Fig. 3. T_1, indicates the potential fusion of sebaceous lipids or of lipids containing cholesterol chains; T_2 is fusion of the lipidic chain inserted in the bilamellate structure, together with some nonpolar material; T_3 is rupture between the associations of lipid polar heads, together with the breakage of cholesterol rigid regions, or attributed to a lipid-protein transition associated with the cell membrane; and T_4 is denaturation of intracellular keratin. On treatment of the stratum corneum with Laurocapram, T_1, T_2, and T_3 are no longer seen in the thermogram; because T_4 is not altered, it is assumed that no significant amount enters the cells; hence, there is no interaction with intracellular proteins. Because Laurocapram is a nonpolar material, it is assumed that it inserts itself between the lipids, avoiding the crystallization of their chains.

On the other hand, Hirvonene et al. (1994) performed researches by DSC in the SC of rabbit atria, human abdomen, and serpent back (extracted with trypsin). The thermogram presents four endothermic peaks at 35, 70, 80, and 90°C, of which the first two correspond to lamellate lipidic structures (according to X-ray diffraction), the third corresponds to protein-associated lipids, and the fourth corresponds to proteins. In contrast with Barry (1987), he found that protein enthalpy is very low (for humans); however, with Laurocapram pretreatment, the first three peaks disappear, so he concludes, like Barry (1987), that there is a rupture of the SC lipidic bilayer structure.

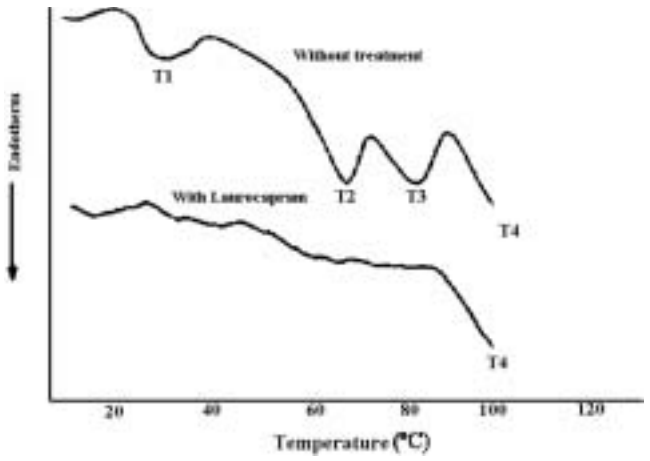

FIGURE 3 Stratum corneum´s DSC. Effect of Laurocapram

Katsu et al. (1989) investigated the action of Laurocapram in human erythrocytes, measuring the hemolysis, the osmotic pressure, and the total amount of phospholipid content, and performing an additional assay for the determination of the transition temperature of a dipalmitoyl phosphatidilcholine (DPPC) artificial liposomal membrane by fluorescent polarization. The results show that Laurocapram penetrates into the lipidic bilayers, increasing the motion of the alkylic chains of lipids due to its dodecyl group. This was determined by measuring the transition temperature of DPPC. Osmotic pressure studies indicate that Laurocapram induces hemolysis and damages the biological membranes, releasing phospholipid fragments. Laurocapram's dodecyl group penetrates into deep regions of the membrane, and the amide group is preferably located near the hydrophilic regions of lipids; the great volume of the ε-caprolactam ring pushes the lipid polar heads upward, deforming their structure, which causes, on accumulation, the release of membrane fragments and the promotion of permeability, both in the erythrocyte and stratum corneum membranes.

On the other hand, Lewis and Hadgraft showed, by means of Langmuir isotherms, that Laurocapram has a cross-sectional molecular area of 60 $Å^2$ (Lewis & Hadgraft, 1990; Hadgraft et al., 1996). Laurocapram inserts itself into the bilayer and seems to push some of the ceramide group heads, leaving a certain volume free, a region in which the alkylic chain increases the disturbance. Therefore, the diffusion process is facilitated, and Laurocapram acts as an enhancer of molecular transference through the skin. The insertion of Laurocapram tends to separate ceramides by electrostatic repulsion due to its positively charged ring (Fig. 2).

Schückler & Lee (1991) studied the compression on a monomolecular film of cholesterol, ceramide, and a mixture of six fatty acids of the SC (stearic, palmitic, myristic, oleic, linoleic, and palmitoleic acids). Laurocapram reduces the condensation state of these films, consistently with the fluidity increase within the monolayers. In addition, Laurocapram slightly alters

the transepidermal water loss (TEWL) from the monomolecular lipid layer.

In 1993, Schückler et al. performed studies by DSC and X-ray diffraction by using two models or matrixes: matrix I (M_I) consisted of SC lipids, principally fatty acids (stearic, palmitic, myristic, oleic, linoleic, and palmitoleic acid), showed a diffraction pattern characteristic of a mixed hexagonal and lamellar structure; matrix II (M_{II}) consisted of SC lipids (the same as M_I more cholesterol and ceramides, in a ratio of 31:25:44), and the pattern indicated a lamellar structure; both matrixes were with 32% water. Laurocapram 0–50% was incorporated into each matrix. The results show that with Laurocapram 30%, the hexagonal periodicity of M_I is attenuated, and this seems to be accompanied by the lamellate transition of phase H_{II}, which is consistent with the hypothesis of a reverse hexagonal phase. In matrix II (M_{II}), no transition occurs at the lamellate structure, maybe because of the molecular geometry of Laurocapram, which has a large head compared with the volume of its alkylic chain. With M_I, the temperature and enthalpy of the endothermic transition of fatty acids are reduced with the increase of the enhancer's concentration, and they are hardly altered for M_{II}.

Hadgraft et al. (1996) suggest that Laurocapram introduces itself into the lamellate bilayer, causing the rupture of the lipid packing. The polar head is embedded in the polar moiety of lipids, fluidizing them, reducing the microviscosity, and increasing the diffusion coefficient. When Laurocapram is combined with other promoters, the effect is greater, causing a disruption between the skin lipids and increasing fluidity and permeation. The promoter activity is associated with the molecular geometry, the charge distribution, concentration, and temperature; these parameters are very important for the classification of this type of compounds as enhancers or retarders (Ermolina et al., 2000).

The conformation adopted by Laurocapram depends on the head group in the interaction with the contiguous molecules (Lewis & Hadgraft, 1990). The hydrogen bridges of the lipid head groups are an important factor for the membrane's stability; therefore, when Laurocapram inserts itself into the intercellular lipids, it is suggested that hydrogen bridges are formed with an adjacent molecule, leaving a free space at the opposite position and creating a fluidity region (Hadgraft, 1996; Michniak, 1995; Lewis & Hadgraft, 1990; Hadgraft et al., 1996; Schückler & Lee, 1991). Table 2 summarizes the mechanisms proposed by different authors, some of which have already been mentioned.

LAUROCAPRAM FORMULATIONS AND STUDIES PERFORMED

In the last years, a large number of studies have been carried out by using formulations with Laurocapram, including various vehicles and drugs, to evaluate their enhancer action. The effect of Laurocapram has been evaluated, on one hand, in in vitro studies, by using diffusion cells or by skin isolation and perfusion, on the other hand, by performing in vivo permeation studies, through the tape-stripping technique (removal of the stratum corneum with adhesive tape), radioactive markers, drug recovery in the skin's surface, evaluation of a biological or pharmacological effect, determination of the amount of drug in the general circulation or excreted (mainly in the feces and urine), autoradiograph, skin biopsies, and infrared spectroscopy.

TABLE 2 **Mechanisms of Action for Laurocapram**

Proposed mechanism of action	References
Disruption of the lipidic bilayer. Laurocapram does not enter into the cells in significant amounts.	Barry, 1987; Hirvonene et al., 1994
Laurocapram penetrates into the lipidic bilayers, increasing the motion of the alkylic chains of lipids due to its dodecyl group; the ε-caprolactam ring pushes the lipid polar heads, deforming them and promoting permeability.	Katsu et al., 1989
It increases the fluidity and permeation in the lipidic regions of human skin. It fluidizes the hydrophobic regions of the lamellate structure.	Allan, 1995; Hirvonene et al., 1994; Schückler & Lee, 1991; Schückler et al., 1993; Beastall et al., 1998

Some of the results of these studies are summarized in Table 3, which presents the most relevant results from 1984 to 2005 and makes evident the great interest for Laurocapram as an enhancer. As can be seen, the techniques used to prove its action, as well as the animal models tested, are varied.

As shown in Table 3, Laurocapram promotes the permeation of most drugs, whether of lipophilic or hydrophilic nature (Hadgraft & Williams, 1993), and in some cases, there is even an increase of the biological or pharmacological effect of drugs when applied with Laurocapram. However, recent studies show that in some instances the application of Laurocapram has not the expected enhancer effect [e.g., 5-(2-bromovinyl)-2-deoxyuridine (BVDU) and cidofovir (Afouna et al., 2003; Afouna, 2001)]; in the case of morphine chlorhydrate, the iontophoretic transport is not increased, but less electric current is required (Numajiri et al., 1998).

In other instances, there are discrepancies among authors, because some of them report an increase of the drugs' flux, and other authors even report a reduction. For example, in the case of estradiol, Morgan et al. (1998) report an increase (animal model: pig skin), and Nicolazzo et al. (2004) report a reduction, pointing out that it is retained in the membrane (animal model: pig oral mucosa). A similar case is that of flurbiprofen, because Akhter and Barry (1984) mention an increase in the flux of this drug when Laurocapram is added with dimethyl sorbide or propylene glycol, but not with Laurocapram and sorbitol (animal model: human skin). In contrast, Fang et al. (2003) report a reduction in flurbiprofen's flux (animal model: rat skin). A special case is that of acyclovir; Kumar et al. (1987) report a reduction of deaths caused by herpes simplex in pigs when acyclovir is applied with Laurocapram. However, Afouna et al. (2001, 2003) who treated mice infected with skin herpes virus type 1, report that although the drug flux increases, the antiviral efficacy is almost null.

In general, a synergic enhancing effect is reported when Laurocapram is combined with a solvent, particularly with propylene glycol (Barry, 1987; Akhter & Barry, 1984; Phillips & Michniak, 1995; Michniak et al., 1998). A very particular case is that of caffeine, whose flux is increased when the skin is pretreated with Laurocapram 0.4 M in propylene glycol (Phillips and Michniak, 1995), which, however, does not increase when Laurocapram 5% is applied in ethanol (Nicolazzo et al., 2004), despite the well-known promoter effectiveness of ethanol. However, when comparing the results of these two studies, it should be taken into account that the animal model used was different, using hairless mouse skin in the first case and pig buccal mucosa in the second case; therefore, the effect observed cannot be attributed exclusively to the change of the solvent containing Laurocapram. The enhancing effect of Laurocapram is also increased when it is combined with enhancers of physical type, such as iontophoresis or ultrasound (Numajiri et al., 1998; Ganga et al., 1996; Gao & Liang, 1998; Fang et al., 1999; Kanikkannan et al., 2000; Meidan et al., 1998, 2003).

When drugs are ionized, they are hardly able to cross the permeability barrier, constituted by the stratum corneum. In Laurocapram, it has been observed that with some active agents, particularly with sodium salicylate (Hadgraft et al., 1985), it forms ionic pairs, increasing permeation.

It is important to highlight that the enhancing effect of Laurocapram is observed both when it is applied in a solution and when it is formulated in a pharmaceutical form, either in patches, cream, gel, or ointment-gel (Khaled et al., 2001; Fang et al., 1999; Ogiso et al., 1987; Escobar-Chávez et al., 2005). In addition, it is interesting to note that the promoting effect of Laurocapram has been proven in the skin of different species of animal models, as well as in human skin and buccal mucosa (Khaled et al., 2001; Allan, 1995; Barry 1987; Wiechers et al., 1990b; Wiechers et al., 1990c; Hadgraft & Williams, 1993; Afouna, 2001; Numajiri et al., 1998; Morgan et al., 1998; Akhter & Barry, 1984; Fang et al., 2003; Phillips & Michniak, 1995; Michniak et al., 1998; Ganga et al., 1996; Meidan et al., 1998; Ogiso et al., 1987; Sekine et al., 1987; Kurosaki et al., 1989; Monti & Saettone, 1997; Bai & Luo, 1999; Xing et al., 2000; Cato et al., 2001; Puglia et al., 2001; Yang & Yi, 2001; Demierre et al., 2003; Bennett et al., 1984; Ruland et al., 1994, 1994b; Turnen et al., 1994; Akimoto et al., 1996; Squillante et al., 1998; Smith & Irwin, 2000; Cato et al., 2001; Fang et al., 2001; Liu & Zhou, 2001; Xu et al., 2002).

Table 4 shows the flux values (J) obtained for different drugs, using Laurocapram and its derivatives as enhancers. The flux values (J) correspond to the amount of drug that crosses a known area of the membrane (e.g., the skin), by time unit. These flux values are derived from Fick's equations, considering that the

TABLE 3 **Drugs Tested With Laurocapram (Azone®) and Results Obtained**

Drug	Technique used for evaluation	Animal model	Results	References
Propranolol hydrochloride	Diffusion cells	Rabbit skin	↑ penetration	Khaled et al., 2001
Metothrexate	Disease evaluation and serum quantification	Humans affected	Local action is observed. ↑ penetration	Allan, 1995
Cidofovir	In vitro (diffusion cells) In vivo (evaluating the antiviral efficacy)	In vitro, hairless mouse skin. In vivo, mice infected with HSV-1	In vitro, the drug's flux is similar with or without AZO, but the antiviral efficacy increases in vivo	Afouna et al., 2003
Acyclovir	In vitro (diffusion cells) In vivo (evaluating the antiviral efficacy)	In vitro, hairless mouse skin. In vivo, healthy mice and mice infected with HSV-1	In vitro, the drug's flux increases, but the antiviral efficacy is almost null in vivo.	Afouna et al., 2003
Triamcinolone acetonide	Evaluation of therapeutic effect	Humans with topical disease	↑ effectiveness	Wiechers et al., 1990b,c
Metronidazole	In vitro (diffusion cells)	Human stratum corneum	↑ penetration	Hadgraft and Williams, 1993
Acyclovir (ACV) and E 5-(2-bromovinyl)-2-deoxyuridine (BVDU)	In vivo and in vitro (diffusion cells)	Hairless mouse skin	↑ absorption for ACV; no significant increase for BVDU	Afouna, 2001
Morphine chlorhydrate	In vitro (iontophoretic diffusion cell)	Hairless rat skin	It does not increase the iontophoretic transport, but requires less electric current.	Numajiri et al., 1998
Testosterone, estradiol, progesterone, norethindrone acetate	In vitro (diffusion cells)	Pig skin	↑ penetration	Morgan et al., 1998
Caffeine	In vitro (diffusion cells)	Pig buccal mucosa	It does not increase flux	Nicolazzo et al., 2004
Estradiol	In vitro (diffusion cells)	Pig buccal mucosa	Causes a 67.6% reduction in flux, and the drug is retained in the membrane	Nicolazzo et al., 2004
Triamcinolone acetonide	In vitro (diffusion cells)	Pig buccal mucosa	4.1-fold increase in permeability, 2.4-fold increase in the partition coefficient buccal mucosa-buffer	Nicolazzo et al., 2004
Flurbiprofen	In vitro (diffusion cells)	Human skin	↑ flux	Akhter and Barry, 1984
Flurbiprofen	In vitro (diffusion cells) In vivo (TEWL, colorimetry, and histological examination)	Rat skin	In vitro, the drug's flux decreases; in vivo, erythema and moderate irritation occur; there is a 2-fold increase in the TEWL and an 8.4-fold increase in the colorimetric factor; histologically, neutrophils and lymphocytes increase	Fang et al., 2003

(Continued)

TABLE 3 (Continued)

Drug	Technique used for evaluation	Animal model	Results	References
Acyclovir	Disease evaluation	Small guinea pigs infected with herpes simplex virus	The number of deaths decreased from 50 to 22%	Kumar et al., 1987
5-Fluorouracil, caffeine, ibuprofen, salicyluric acid, salicylic acid, and triamcinolone acetonide	In vitro (diffusion cells)	Hairless mouse skin	↑ flux	Phillips and Michniak, 1995
Hydrocortisone	In vitro (diffusion cells)	Hairless mouse skin	↑ penetration	Michniak et al., 1998
Metoprolol tartrate	In vitro (diffusion cells, iontophoretic device)	Human cadaver skin	AZO causes a 130-fold increase in flux with iontophoresis	Ganga et al. 1996
Piroxicam, indomethacin, naproxen, diclofenac	In vitro (diffusion cells)	Not reported	↑ iontophoretic transport of ionized drugs	Gao and Liang, 1998
Enoxacin	In vitro (diffusion cells) In vivo (microdialysis)	Wistar rats' skin	Increases the enoxacin residues in the skin, similar in vivo	Fang et al., 1999
Timolol maleate	Induction of tachycardia, measurement of isoprenaline sulfate inhibited by electrocardiogram	Rabbits	↑ transdermal release	Kanikkannan et al., 2000
Buspirone hydrochlorhydrate	In vitro (diffusion cells, iontophoresis)	Human skin	AZO causes a 27-fold increase in flux, and with iontophoresis, a 87-fold	Meidan et al., 2003
Hydrocortisone	In vitro, ultrasound	Rat skin	↑ transport	Meidan et al., 1998
Sodium salicylate	In vitro (diffusion cells)	Membranes with artificial lipids	AZO forms ionic pairs with salicylate promoting its transport	Hadgraft et al., 1985
Dexamethasone acetate or dexamethasone palmitate	Evaluation of absorption and plasma quantification	Rat skin	They are quickly absorbed, high percentage in the circulation.	Ogiso et al., 1987
Verapamil	Drug release in vitro and transdermal absorption in vivo	Rat skin	A more than 10-fold increase in verapamil plasma levels	Sekine et al., 1987
Salicylic acid	In vivo, plasma quantification	Hamster (buccal mucosa)	AZO causes a 2.7-fold increase of absorption	Kurosaki et al., 1989
Propafenone hydrochloride	In vitro (diffusion cells)	Hairless mouse skin	Constant release beyond 48 h	Monti and Saettone, 1997
Tinidazole	In vitro (diffusion cells)	Mouse skin	↑ penetration	Bai and Luo, 1999
Naproxen	In vitro (diffusion cells) Ex vivo (perfusion)	In vitro: Human abdominal skin. *Ex vivo*: Rabbit ear skin	↑ penetration	Degim et al., 1999
Ketoprofen	In vitro (diffusion cells)	Mouse skin	↑ penetration	Fu et al., 1999

(Continued)

TABLE 3 **(Continued)**

Drug	Technique used for evaluation	Animal model	Results	References
Zinc gluconate	In vivo (serum quantification)	Rabbit	Adequate formulation for cutaneous absorption	Liu et al., 1999
5-Fluorouracil	Ultrasound in diffusion cells	Wistar rats' skin	AZO alone increases diffusion more than ultrasound	Meidan et al., 1999
Indomethacin	In vitro (diffusion cells)	Rat skin	↑ penetration	Xing et al., 2000
Triamcinolone acetonide	In vivo, vasoconstriction studies	Humans	↑ penetration	Cato et al., 2001
Clonazepam or Lorazepam	In vitro (diffusion cells)	Human skin: epidermis and stratum corneum	↑ flux	Puglia et al., 2001
Aspirin	In vitro (diffusion cells)	Mice abdomen skin	↑ penetration at high pHs (8.0)	Yang and Yi, 2001
Methotrexate	Disease evaluation and adverse effects	Human subjects with mycosis	Local action is seen, safe and well tolerated treatment	Demierre et al., 2003
Sodium Naproxen	In vivo	Human skin	↑ flux	Escobar-Chávez et al., 2005
Betamethasone-17-benzoate	Vasoconstriction and bioavailability studies	Humans	↑ vasoconstriction and bioavailability	Bennett et al., 1984
Melanotropin (tetrapeptide)	In vitro (diffusion cells)	Human skin or hairless mouse skin	↑ penetration	Ruland et al., 1994a, b
AZO in ethanol	In vitro (diffusion cells)	Human buccal mucosa	↑ penetration	Turnen et al., 1994
Indomethacin	In vitro (diffusion cells)	Mouse skin	Damage to the skin was observed	Akimoto et al., 1996
Nifedipine	In vitro (diffusion cells)	Hairless rat skin	Flux is 4 times greater than the oral route	Squillante et al., 1998
Salicylic acid	In vitro (diffusion cells)	Human skin and rubber membrane	↑ salicylic acid permeation at pH 4 and 7.2	Smith and Irwin, 2000
Triamcinolone acetonide	Disease evaluation	Humans with atopic dermatitis	Improvement of the signs and symptoms (erythema and pruritus)	Cato et al., 2001
Indomethacin	In vitro (diffusion cells) and skin histological examination	Hairless mouse skin	↑ penetration	Fang et al., 2001
Aminophylline	In vitro (diffusion cells)	Rat skin	↑ penetration	Liu and Zhou, 2001
Galanthamine hydrobromide	In vitro (diffusion cells)	Not reported	↑ penetration	Xu et al., 2002
Benazepril and hydrocortisone	In vitro (diffusion cells)	Hairless mouse skin	↑ penetration	Tenjarla et al., 1999
Chrysophanic acid	In vitro (diffusion cells)	Mouse skin	↑ penetration at pH 4.0	Yu et al., 1999
Antipyrine, 5-fluoroacil, 2-phenyl ethanol and 4-phenyl butanol	In vitro (diffusion cells)	Wistar rats' skin	↑ penetration	Lopez et al., 2000; Lopez–Casteilano et al., 2000
Furosemide	In vitro (diffusion cells)	Human epidermis	↑ flux	Agyralides et al., 2004

(Continued)

TABLE 3 (Continued)

Drug	Technique used for evaluation	Animal model	Results	References
Progesterone	In vitro (diffusion cells)	Synthetic lipophilic membranes	↑ amount of drug absorbed in the membrane	Zaprutko et al., 2004
Ondansetron	In vitro (diffusion cells)	Human epidermis	↑ flux	Dimas et al., 2004
Imperatorin	In vitro (diffusion cells)	Mouse, rabbit, rat and human skin	4.9-fold increase in the permeability coefficient	Lu and He, 2003
Triamcinolone acetonide	In vitro (diffusion cells)	Porcine buccal mucosa	↑ flux and tissue concentration	Nicolazzo et al., 2005
Theophylline	In vitro (diffusion cells)	Human skin	Aqueous donor vehicle enhancement ratio 2.2 ± 0.7 and isopropyl-myristate suspension AZO was inactive.	Vávrová et al., 2005
5-Fluorouracil	In vitro (diffusion cells)	Human stratum corneum	24-fold increase in permeability	Singh et al., 2005

(AZO), Laurocapram = Azone®; (TEWL), transepidermal water loss; (ACV), acyclovir and (BVDU) E 5-(2-bromovinyl)-2-deoxyuridine; (↑), increase.

passage of a substance across the stratum corneum occurs by passive diffusion (Alberty and Hadgraft, 1979a, b).

When the skin is treated with a substance and the flux value of a drug increases in relation to a control (nontreated skin), it is said that the substance in question exerts an enhancing effect by facilitating the passage of the drug through the skin. When the flux value of a drug is known (with and without the presence of an enhancer), it is possible to quantitatively evaluate the "enhancing" effect of the substance.

As mentioned, Laurocapram contains a long alkylic chain limited by a polar cycle called azacycloheptan-2-one (Naik & Guy, 1997). In the studies by Hoogstrate, a maximum flux is seen when this alkylic chain has 12 carbons. In this way, the flux, and consequently the enhancing effect, are reduced when the alkylic chain is extended or shortened (Hoogstrate et al., 1991).

As seen in Table 4, the flux of a large number of drugs is dramatically increased when the skin is pretreated with Laurocapram, or when it is directly used in the formulation (Afouna et al., 2003; Akhter & Barry, 1984; Phillips & Michniak, 1995; Ganga et al., 1996; Meidan et al., 2003; Degim et al., 1999; Meidan et al., 1999; Ruland et al., 1994a, 1994b; Smith & Irwin, 2000; Fang et al., 2001; Tenjarla et al., 1999; Agyralides et al., 2004; Tenjarla et al., 1996; Niazy, 1996) in other cases, the flux is almost the same or even diminishes (Nicolazzo et al., 2004; Fang et al., 2003), which is consistent with the data reported in Table 3. In addition, its effect is greater than with other enhancers, particularly methanol, propylene glycol, dimethyl isosorbide, and ethanol (Akhter & Barry, 1984; Phillips & Michniak, 1995; Fang et al., 2001; Bosman et al., 1998). It is also observed that the flux values of drugs increase with the increase of the Laurocapram proportion (Ruland et al., 1994a).

LAUROCAPRAM'S TOXICITY

Studies have been performed in mice, rats, pigs, rabbits, and monkeys, and no systemic adverse effects or dermal toxicity have been found after 1 month of skin exposition. In single-dose oral toxicity studies, the LD_{50} with Laurocapram 100% is 7.4 and 9 g/kg in mice and rats, respectively. By dermal route, applying Laurocapram 100% in rats, the LD_{50} is 7.3 g/kg. By ocular route, it causes mild irritation at high concentrations; with prolonged doses, it causes mild conjunctival hyperemia in rabbits (Allan, 1995).

Studies were carried out with some Laurocapram derivatives in which the number of carbons in the alkylic chain was changed, and it was found that in human epidermal cells, toxicity increases when the chain is lengthened from 2 to 8 carbons, it remains constant between 8 and 14 carbons, and it is again reduced when the chain's

TABLE 4 **Flux Values Obtained for Different Drugs When Laurocapram (Azone®) Is Used As Enhancer**

-	Membrane model	Treatment or formulation	J (μg/cm^2 h)	References
Cidofovir	Hairless mouse skin	Control: 0.5 % drug, 1% HPC, and DMSO	6.048 ± 0.2016	Afouna et al., 2003*
		Control: 0.1% drug, 1% HPC, and DMSO	1.310 ± 0.302	
		Formulation: 0.25% drug, 5% AZO, 1% HPC, and DMSO	3.679 ± 0.806	
		Formulation: 0.5% drug, 5% AZO, 1% HPC, and DMSO	5.140 ± 2.066	
		Formulation: 1% drug, 5% AZO, 1% HPC, and DMSO	12.247 ± 1.764	
		Formulation: 5% drug, 5% AZO, 1% HPC, and DMSO	21.722 ± 3.528	
Acyclovir		Control: 0.1% drug, 1% HPC, and DMSO	0.605 ± 0.050	
		Formulation: 0.1% drug, 5% AZO, 1% HPC, and DMSO	1.058 ± 0.050	
Flurbiprofen deposited in film	Human skin	Control: Film + drug	3.9	Akhter & Barry, 1984
		Film with drug + dimethyl isosorbide	3.7	
		Film with drug + dimethyl isosorbide + AZO	6.2	
Flurbiprofen deposited in film		Control: Film + drug	17	
		Film with drug + PG	27	
		Film with drug + PG + AZO	56	
Flurbiprofen deposited in film		Control: Film + drug	11	
		Film with drug + Solketal	9.4	
		Film with drug + Solketal	4.2	
Flurbiprofen in hydrogel	Rat skin	Control: 1% drug in citrate-phosphate buffer pH = 7	8.27 ± 1.07	Fang et al., 2003
		Control: 1% drug in hydrogel	6.21 ± 0.65	
		Formulation: 1% drug, 5% AZO in hydrogel	5.54 ± 0.45	
5-Fluorouracil in PG	Mouse skin	Skin pretreated with methanol	3.12 ± 1.01	Phillips & Michniak, 1995
		Skin pretreated with methanol in PG	3.32 ± 0.78	
		Skin pretreated with AZO 0.4 M in PG	49.6 ± 9.36	
Caffeine in PG		Skin pretreated with methanol	0.56 ± 0.06	
		Skin pretreated with methanol in PG	0.67 ± 0.18	
		Skin pretreated with AZO 0.4 M in PG	4.22 ± 0.94	
Ibuprofen in PG		Skin pretreated with methanol	95.40 ± 13.71	
		Skin pretreated with methanol in PG	90.60 ± 10.30	
		Skin pretreated with AZO 0.4 M in PG	108 ± 8.5	

(Continued)

TABLE 4 (Continued)

-	Membrane model	Treatment or formulation	J ($\mu g/cm^2$ h)	References
Salicyluric acid in PG		Skin pretreated with methanol	88.4 ± 17.0	
		Skin pretreated with methanol in PG	79.5 ± 13.0	
		Skin pretreated with AZO 0.4 M in PG	331 ± 47.9	
Salicylic acid in PG		Skin pretreated with methanol	118 ± 26.7	
		Skin pretreated with methanol in PG	70.1 ± 10.5	
		Skin pretreated with AZO 0.4 M in PG	93.0 ± 4.2	
Triamcinolone acetonide in PG		Skin pretreated with methanol	0.08 ± 0.01	
		Skin pretreated with methanol in PG	0.07 ± 0.001	
		Skin pretreated with AZO 0.4 M in PG	1.25 ± 5.66	
Metoprolol	Human epidermis	Control	10.39 ± 3.17	Ganga et al., 1996
		Pretreatment with AZO	83.47 ± 10.20	
Buspirone hydrochlorhydrate		Control: 2% drug	1.9 ± 0.6	Meidan et al., 2003
		Control: 2% drug and iontophoresis 0.025 mA/cm^2	56.1 ± 44.9	
		Formulation: 2% drug and AZO, 2.5%	51.9 ± 10.4	
		Formulation: 2% drug, 2.5% AZO, and iontophoresis 0.025 mA/cm^2	166.1 ± 19.4	
Naproxen	Abdominal human skin	Control	1.07 ± 0.03	Degim et al., 1999
		AZO 3% in ethanol	2.84 ± 0.11	
Naproxen	Rabbit ear	Control	0.34 ± 0.03	
		AZO 3% in ethanol	1.51 ± 0.04	
5-Fluorouracil	Wistar rat skin	Control	5.46×10^{-5}	Meidan et al., 1999*
		AZO in ethanol 1%	2.39×10^{-4}	
Melanotropin (Hisetal)	Hairless mouse skin	Control	0.22	Ruland et al.,1994a*
		AZO in PG 3%	1.82 ± 0.02	
		AZO in PG 5%	3.98 ± 0.17	
Melanotropin (Hisetal)	Human skin	Control	0.043	Ruland et al.,1994b*
		Skin pretreated with AZO in PG 5%	0.17 ± 0.02	
		AZO included in the formulation with the drug	0.14 ± 0.04	
Salicylic acid-saturated suspension, donor pH = 4.04, receptor pH = 3.40	Human skin	Control	88.38 ± 11.05	Smith & Irwin, 2000
		PG	89.76 ± 4.56	
		AZO in PG 0.5 M	146.38 ± 2.90	

(Continued)

TABLE 4 **(Continued)**

-	Membrane model	Treatment or formulation	J (μg/cm^2 h)	References
Salicylic acid-saturated suspension, donor pH = 4.04, receptor pH = 7.22		Control	89.76 ± 22.51	
		PG	109.1 ± 1.93	
		AZO in PG 0.5 M	226.48 ± 21.40	
Indomethacin 1% in ethanol/pH 7.4	Hairless mouse skin	Control: Ethanol/water (1:1)	15.47 ± 4.13	Fang et al., 2001
		AZO 3% in ethanol/water (1:1)	69.32 ± 11.35	
Benazepril	Hairless mouse skin	Control	10.90 ± 1.80	Tenjarla et al., 1999
		AZO in PG 3%	500.6 ± 89	
Hydrocortisone		Control	2.70 ± 1.10	
		AZO in PG 3%	59.60 ± 11.10	
Furosemide	Human epidermis	Control: Drug 8.48 mg/mL,[a] 1% HPC 1%	0.234 + 0.024[b] 0.284 + 0.026[c]	Agyralides et al., 2004
		Control: Drug 8.48 mg/mL,[a] 1.25% HPC	0.176 + 0.031[b] 0.216 + 0.039[c]	
		Control: Drug 8.48 mg/mL,[a] 1.50% HPC	0.144 + 0.027[b] 0.206 + 0.031[c]	
		Control: Drug 16.96 mg/mL,[a] 1.25% HPC	0.336 + 0.058[b] 0.422 + 0.063[c]	
		Formulation: Drug 11.26 mg/mL,[a] 1% HPC, and 5% AZO	6.526 + 0.437[b] 5.875 + 0.571[c]	
		Formulation: Drug 11.26 mg/mL,[a] 1.25% HPC, and 5% AZO	5.843 + 0.481[b] 5.508 + 0.269[c]	
		Formulation 2: Drug 11.26 mg/mL,[a] 1.25% HPC, and 5% AZO	5.880 + 0.443[b] 6.162 + 0.269[c]	
		Formulation: Drug 11.26 mg/mL,[a] 1.5% HPC, and 5% AZO	6.210 + 0.618[b] 5.503 + 0.513[c]	
		Formulation: Drug 14.85 mg/mL,[a] 1% HPC, and 10% AZO	3.365 + 0.625[b] 3.438 + 0.656[c]	
		Formulation: Drug 14.85 mg/mL,[a] 1.25% HPC, and 10% AZO	3.723 + 0.308[b] 3.457 + 0.585[c]	
		Formulation: Drug 14.85 mg/mL,[a] 1.25l% HPC, and 10% AZO	3.588 + 0.607[b] 3.846 + 0.752[c]	
		Formulation: Drug 14.85 mg/mL,[a] 1.5% HPC, and 10% AZO	3.523 + 0.553[b] 3.306 + 0.485[c]	
		Formulation: Drug 13.83 mg/mL,[a] 1.25% HPC, 5% AZO, and 5% oleic alcohol	8.356 + 0.669[b] 8.654 + 1.060[c]	
		Formulation: 14.02 mg/mL,[a] 1.25% HPC, 5% AZO, and 10% oleic alcohol	5.708 + 0.808[b] 6.658 + 1.130[c]	

(Continued)

TABLE 4 (Continued)

-	Membrane model	Treatment or formulation	J (μg/cm^2 h)	References
		Formulation: 16.38 mg/mL,[a] 1.25% HPC, 10% AZO, and 5% oleic alcohol	7.442 + 0.613[b] 8.154 + 0.860[c]	
		Formulation: 18.27 mg/mL,[a] 1.25% HPC, 10% AZO, and 10% oleic alcohol	7.520 + 0.509[b] 7.904 + 0.533[c]	
Aminoacid 9-deglycinamide, 8-arginine vasopressin	Stratum corneum	Control	1.35 ± 0.53	[Hoogstrate et al., 1991
		PG	1.02 ± 0.20	
		Pretreatment with C14-AZO 0.15 M in PG	3.30 ± 0.23	
		Pretreatment with C12-AZO 0.15 M in PG	4.75 ± 0.48	
		Pretreatment with C10-AZO 0.15 M in PG	2.52 ± 0.15	
		Pretreatment with C8-AZO 0.15 M in PG	1.37 ± 0.15	
		Pretreatment with C6-AZO 0.15 M in PG	0.09 ± 0.05	
Terbutaline	Rabbit skin	Control	8.30 ± 2.30	Tenjarla et al., 1996
		AZO 3%	28.50 ± 6.20	
Terbutaline	Guinea pig skin	Control	7.70 ± 1.90	
		AZO 3%	56.10 ± 6.60	
Terbutaline	Complete human skin	Control	0.60 ± 0.10	
		AZO 3%	3.60 ± 0.80	
Terbutaline	Human epidermis	Control	1.60 ± 0.40	
		AZO 3%	6.50 ± 1.80	
Dihydroergotamine	Human skin	Control: Drug in PG	0.045 ± 0.013	Niazy, 1996
		Formulation: Drug/PG/ AZO 6%	2.455 ± 0.203	
Dihydroergotamine	Rat skin	Control: Drug in PG	0.270 ± 0.026	
		Formulation: Drug/PG/ AZO 6%	11.343 ± 1.117	
Dihydroergotamine	Guinea pig skin	Control: Drug in PG	0.395 ± 0.042	
		Formulation: Drug/PG/ AZO 6%	7.927 ± 0.569	
Dihydroergotamine	Rabbit skin	Control: Drug in PG	0.128 ± 0.021	
		Formulation: Drug/PG/ AZO 6%	32.188 ± 2.757	
Dihydroergotamine	Hairless mouse skin	Control: Drug in PG	10.035 ± 1.177	
		Formulation: Drug/PG/ AZO 6%	144.887 ± 23.516	
Atropine	Pig skin	Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	92.88 ± 23.73	Bosman et al., 1998
Atropine sulphate H_2O		Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	31.96 ± 7.64	
Benzotropine mesylate		Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	86.76 ± 9.68	

(Continued)

TABLE 4 (Continued)

-	Membrane model	Treatment or formulation	J (μg/cm^2 h)	References
Deoxythymide HCl		Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	23.51 ± 13.95	
Oxyphencyclimine HCl		Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	20.92 ± 11.79	
Scopolamine HBr·3H2O		Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	27.72 ± 15.45	
Tropicamide		Formulation: Phosphate buffer pH = 7.4, ethanol, PG, and AZO	36.920 ± 23.856	

(PG), propylene glycol; (C6), 6 carbon alkylic chain; (C8), 8 carbon alkylic chain; (C10), 10 carbon alkylic chain; (C12), 12 carbon alkylic chain; (C14), 14 carbon alkylic chain; (AZO), Laurocapram = Azone®; (HPC), hydroxypropylcellulose; (DMSO), dimethyl sulfoxide.

*Calculated from the data included in the article.

[a]Amount calculated according to the drug's solubility in the vehicle (ethanol 60%, glycerin 15%, enhancer 5 or 10%, and water q.s. for 100%).

[b]Flux determined at 24 h.

[c]Flux determined at 48 h.

length is increased. A similar trend is observed with flux by using nitroglycerin as active agent, which suggests a relationship between toxicity and the penetration-enhancing effect (Ponec et al., 1989, 1990). In multiple-dose studies (30 applications) by dermal route, with concentrations between 10 and 50% in hairless mice, it is slightly irritant; in rats, it is very irritant and shows moderate irritation in rabbits and pigs. When applied for 6 months at concentrations of 5%, it causes moderate irritation in mice, rats, and monkeys with nonsystemic effects, and moderate changes in the skin are noted. In rats and mice, no tumors or carcinogenic effects have been found, except by oral/nasal route in rats, where cells with tumors have been found, although they are not statistically representative. It also does not show genotoxic, teratogenic, or embryotoxic effects.

Clinical studies have shown that human skin tolerates repeated Laurocapram applications for long periods of time (Wiechers et al., 1987), because it is quickly eliminated from the circulation, and the trend toward irritation is due to the use of high concentrations of Laurocapram with occlusive patches on the application site. Fang et al. (2003) observed that, when Laurocapram 0.0015% is applied to human skin fibroblasts, it induces the production of E2 prostaglandins, but when the concentration is increased to 0.0025%, it does not induce the production of E2 prostaglandins, which may indicate cytotoxicity. One application of Laurocapram 100% to human skin, in normal conditions, shows a minimal absorption (<1%), accumulating in the superficial layers of the stratum corneum, which has been observed by means of SC removal and radioactive markers, without detecting it in the blood and with recovery of only 0.005% in the feces (Allan, 1995).

Although Laurocapram has proved to be an effective penetration enhancer when included in different formulations, it has not been widely accepted. It is included in the China Pharmacopea and is currently used in pharmaceutical products in this country. However, it has not been approved by the FDA for pharmaceutical use. In this respect, some aspects should be considered as relevant: Laurocapram can enhance not only the absorption of other compounds but its own absorption (self-absorption enhancement). After repeated application, a steady-state percutaneous absorption of Laurocapram is established. Furthermore, in addition to its action as dermal penetration enhancer, Laurocapram exhibits certain pharmacological activity, for there is some evidence indicating an antiviral effect (Afouna et al., 2003).

LAUROCAPRAM ANALOGUES

Many compounds have been synthesized from Laurocapram to compare and improve its properties, which has resulted in a great number of analogues. Some of the analogues reported by Michniak et al. (1995) are mentioned below.

Lauramide Hexamethylene (Hexahydro–Lauroyl-1H-Azepine) Derivatives

In general, all amides show an increase of penetration in variable degrees, depending on the model and drug used. This is the case of *N*-dodecyl-2-piperidinone and *N*-dodecyl-2-pyrrolidonone, which showed increase in the penetration of hydrocortisone through the stratum corneum, as with Laurocapram (Fuhrman et al., 1997). Usually, large rings and long chains have a greater enhancing effect, as in the case of compound 1 in Fig. 4, hexamethylene lauramide (Mirejovsky and Takrvri, 1986).

Azacycloalkanone Derivatives

Okamoto et al. (1988, 1991) studied azacycloalkanone derivatives with 5-, 6-, and 7-component rings, using guinea pig skin in vitro and 6-mercaptopurine as model drug. It should be mentioned that compounds 2, 3 (Fig. 4), and Laurocapram show primary irritation, signs of erythema and edema after one 24-h application with 100% of the enhancer. Very long (C_{20} or more) hydrocarbonated chains are less effective. An increase in the number of carbonyl groups in the ring also causes a reduction of activity. Other lactamic derivatives of Laurocapram (Michniak et al., 1993a, b) were evaluated in vitro by using hairless mouse skin. The results showed that derivatives 4 and 5 (Fig. 4) are more effective in the promotion of drug absorption, because they exhibited similar concentrations in the receptor compartment at 24 h, compared with those obtained with Laurocapram. It is important to mention that the amount of drug retained in the membrane was much greater for the lactamic derivatives than for Laurocapram.

Cyclohexanone Derivatives

Drugs' absorption increases significantly when compounds such as 2,6-dimethylcyclohexanone (6), 2-butylcyclohexanone (7), and 4-t-butylcyclohexanone (8) are used, and a small effect is seen with cyclohexanone and 2-methyl (9) and 3-methyl (10) analogues (Fig. 4). In general, dimethylated derivatives are more effective than methylated derivatives (Akitoshi et al., 1998).

For the type of derivatives shown in Fig. 4, an increase is seen in the enhancing effect when the length of the hydrocarbonated chain increases, reaching a maximum level that subsequently diminishes, with 2-*N*-octyl cyclohexane (11) being the most effective. This behavior was reported for other alkane enhancers, alkanoic acids, and saturated fatty acids. Several authors conclude that cyclohexanone derivatives exert their effect by fluidization and modification of the stratum corneum hydrophobic barrier.

Other Derivatives

Many azacycloalkanes were patented in 1992 by Minaskanian and Peck as transdermal enhancers, such as 1-*N*-dodecyl azacyclohept-3-ene-2-one, 1-*N*-dodecyl azacyclohept-4-ene-2-one, 1-*N*-dodecyl-3-methyl azacyclohept-3-ene-2-one, etc. All of them are recommended for use in different formulations, at concentrations between 1 and 10%. Michniak et al. (1993a, b) selected some analogue compounds of Laurocapram to measure their enhancing action. Of these, the one showing the greatest potency is compound 12 (Fig. 4). Bonina et al. (1991) report other derivatives of the 1-alkyl azacycloalkan-2-one ester of indomethacin, with compound 13 showing the greatest enhancing effect (Fig. 4).

Finally, although the Laurocapram derivatives mentioned act as penetration enhancers, they are not more effective than Laurocapram; in addition, it is confirmed that those presenting a higher enhancing effect also produce greater skin irritation.

CONCLUSIONS

The relevance of Laurocapram as an absorption enhancer lies in the fact that it is one of the few molecules synthesized for this purpose: to act as a promoter. Since it was patented in 1976 (Rajadhyaksha, 1976a–c), it has been one of the most studied substances, and it has even been used as a point of reference for the evaluation of the efficacy of other enhancers. As already discussed in this review, the efficacy of Laurocapram cannot be attributed to a single mode of action. On the contrary, the mechanism is complex, because it is able to interact with both the biological membranes' components (particularly lipids), the drug, and the vehicle containing it. According to the results obtained by several authors, with a few exceptions, Laurocapram is an effective enhancer for a wide range of lipophilic and hydrophilic substances. However, it is not a universal enhancer, and for this reason, a large number of investigators have

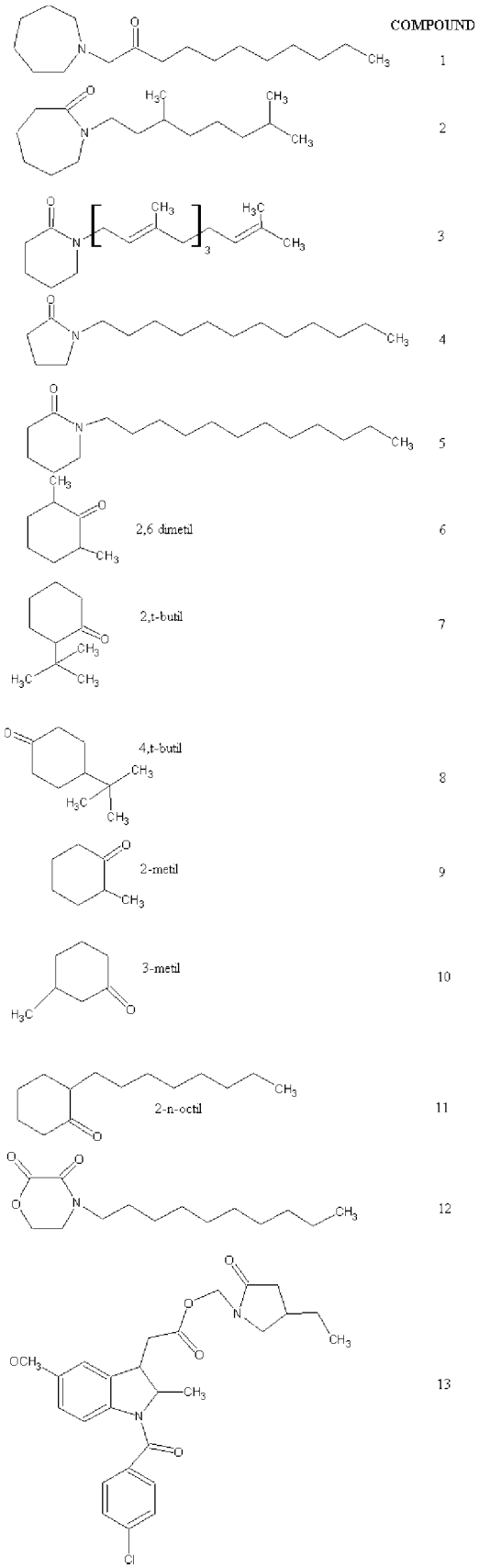

FIGURE 4 **Some laurocapram´s analogues (Mirejovsky and Takrvri, 1986; Okamoto et al., 1988, 1991; Michniak et al., 1993; Akitoshi et al., 1998; Miniskanian and Peck, 1992; Bonina et al., 1991).**

undertaken the task of seeking highly effective derivatives or analogues with low toxic effects. In this arduous search, not all the results have been positive; however, all these efforts have contributed to the establishment of general modes of action for enhancer agents, as well as their structure-activity relationship. Unfortunately, Laurocapram and its derivatives have not been widely accepted for pharmaceutical use because of suspected pharmacological activity or the incertitude about safety.

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