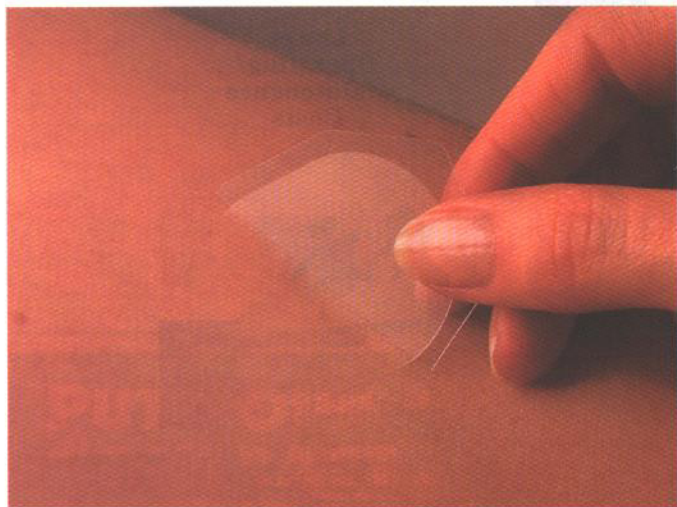


Skin Penetration Enhancers Cited in the Technical Literature

David W. Osborne* and Jill J. Henke



3M DRUG DELIVERY SYSTEMS

A literature review found more than 275 chemical compounds cited as skin penetration enhancers. However, most of the compounds are generally recognized as safe (GRAS) ingredients that would often be considered inert by a formulator. This article lists the chemical substances reported in the technical literature to enhance skin permeation. The reader can view the reference list of more than 400 sources on the *Pharmaceutical Technology* Web site.

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During the development of a topical dosage form, it is often useful to know if solvents or excipients anticipated for use in the formulation have been listed in the literature as skin penetration enhancers. Although recent efforts in using chemical enhancers have focused on substances categorized as generally recognized as safe (GRAS), early work included a wide range of materials. For this reason, a large number of excipients have been claimed to enhance skin penetration. Complete texts concerning pharmaceutical skin penetration enhancement are available and they provide excellent descriptions and critical reviews of this subject (1,2).

The pharmaceutical scientist developing topical products needs to have a quick reference summarizing the skin penetration literature. Topical products often contain many components that are considered inert excipients with respect to the pharmacology and delivery of the active ingredient. Solvents and cosolvents are used to alter drug solubility or ease of processing. Emulsifiers and gelling agents provide the consistency and properties expected of creams, lotions, and gels. Other additives such as antioxidants and preservatives are provided to extend shelf life or ensure quality. The formulator will know the intended use of the excipients present in the formulation, but it is also important to know whether the excipient is suspected of altering pharmacology or delivery. The goal of this review is to list the chemical substances reported in the technical literature to enhance skin permeation. The length of this list is surprising. In a review of the technical and patent literature up to 1996, more than 275 different chemical compounds were found to be cited as skin penetration enhancers. Some of these compounds come from the patent literature in which a series of compounds of custom design were synthesized in hopes of commercializing the ideal chemical enhancer. However, most of the compounds are GRAS ingredients that would often be considered inert by the formulator. By providing this list of supposed penetration enhancers, the authors hope that the formulator will not be surprised by a group of references claiming their "inert" ingredients to be skin penetration enhancers.

Fatty alcohols, fatty acids, and related structures

Fatty alcohols

Aliphatic alcohols (17, 18, 263, 299, 303)
 Decanol (88, 128, 177, 239, 303)
 Lauryl alcohol (dodecanol) (88, 128, 148, 177, 266, 281, 286, 288, 299, 309, 315, 320, 355)
 Linolenyl alcohol (299, 346)
 Nerolidol (402)
 1-Nonanol (239, 242, 298)
n-Octanol (234, 299, 303)
 Oleyl alcohol (31, 97, 98, 155, 199, 246, 381)

Fatty acid esters

Butyl acetate (175, 192)
 Cetyl lactate (58)
 Decyl *N,N*-dimethylamino acetate (312, 315)
 Decyl *N,N*-dimethylamino isopropionate (313)
 Diethyleneglycol oleate (69)
 Diethyl sebacate (68)
 Diethyl succinate (192)
 Diisopropyl sebacate (70)
 Dodecyl *N,N*-dimethylamino acetate (148, 286, 288, 299, 312, 315, 318, 320, 333)
 Dodecyl (*N,N*-dimethylamino)-butyrate (313)
 Dodecyl *N,N*-dimethylamino isopropionate (313, 320)
 Dodecyl 2-(dimethylamino)propionate (148, 280, 284)
 EO-5-oleyl ester (199)
 Ethyl acetate (175, 192, 193, 194, 246, 252, 279)
 Ethylaceto acetate (192)
 Ethyl propionate (192)
 Glycerol monoethers (394)
 Glycerol monolaurate (93, 94, 350, 351, 388)
 Glycerol monooleate (90–94, 388)
 Glycerol monolinoleate (387, 388)
 Isopropyl isostearate (353)
 Isopropyl linoleate (381)
 Isopropyl myristate (46, 101–107, 234, 246, 311, 326, 353)
 Isopropyl myristate/fatty acid monoglyceride combination (391)
 Isopropyl myristate/ethanol/*L*-lactic acid (87:10:3) combination (404)
 Isopropyl palmitate (353)
 Methyl acetate (192, 385)
 Methyl caprate (299)
 Methyl laurate (117, 374, 375, 384)
 Methyl propionate (192)
 Methyl valerate (192)
 1-Monocaproyl glycerol (311)

Monoglycerides (medium chain length) (119)
 Nicotinic esters (benzyl) (129, 130)
 Octyl acetate (252)
 Octyl *N,N*-dimethylamino acetate (312)
 Oleyl oleate (326)
n-Pentyl *N*-acetylprolinate (235, 251)
 Propylene glycol monolaurate (374, 375)
 Sorbitan dilaurate (388)
 Sorbitan dioleate (388)
 Sorbitan monolaurate (388)
 Sorbitan monooleates (48, 50, 346, 388)
 Sorbitan trilaurate (388)
 Sorbitan trioleate (388)
 Sucrose coconut fatty ester mixtures (165, 384)
 Sucrose monolaurate (165)
 Sucrose monooleate (163, 164)
 Tetradecyl *N,N*-dimethylamino acetate (312)

Fatty acids

Alkanoic acids (55, 230, 263, 273, 315, 347)
 Capric acid (57, 299)
 Diacid (262)
 Ethyloctadecanoic acid (401)
 Hexanoic acid (103)
 Lactic acid (109, 110)
 Lauric acid (55, 111, 178, 218, 220, 299, 309)
 Linoelaidic acid (55)
 Linoleic acid (55, 299, 381)
 Linolenic acid (55)
 Neodecanoic acid (55)
 Oleic acid (3, 11, 31, 55, 92, 97, 118, 137, 148, 152, 153, 154, 178, 199, 200, 210, 211, 216, 218, 219, 228, 231, 234, 243, 246, 265, 266, 271, 275, 283, 294–296, 299, 305, 307–309, 320, 323, 333, 341, 344, 346, 356–358, 376, 381)
 Palmitic acid (55)
 Pelargonic acid (55)
 Propionic acid (103)
 Vaccenic acid (88, 128, 177)

Fatty alcohol ethers

α -Monoglyceryl ether (23)
 EO-2-oleyl ether (199)
 EO-5-oleyl ether (199)
 EO-10-oleyl ether (199)
 Ether derivatives of polyglycerols and alcohols (1-*O*-dodecyl-3-*O*-methyl-2-*O*-(2',3'-dihydroxypropyl)glycerol) (85)

cited as penetration enhancers. For compounds with multiple literature citations, such as azone and oleic acid, a representative sampling of the literature rather than an exhaustive or critical listing is provided. Thus, this is not a critical review, but a listing of at least one reference of the chemical compounds cited in the technical or patent literature as skin penetration enhancers.

Throughout this introduction we have used the terms *supposed* and *cited as* skin penetration enhancers. The literature

investigators do not sufficiently characterize a mechanism to establish that the substance is a chemical skin penetration enhancer. By definition, a chemical skin penetration enhancer increases skin permeability by reversibly damaging or by altering the physiochemical nature of the stratum corneum to reduce its diffusional resistance (3). Although there are many strategies to enhance skin penetration, only some of them include the use of chemical skin penetration enhancers. Additives that en-

Miscellaneous compounds and groups

Biologics

L- α -amino-acids (108, 346)
 Lecithin (112, 229, 258, 346, 352)
 Phospholipids (403)
 Saponin/phospholipids (161)
 Sodium deoxycholate (285)
 Sodium taurocholate (285)
 Sodium tauroglycocholate (285)

Enzymes

Acid phosphatase (332)
 Calonase (310)
 Orgelase (310)
 Papain (346)
 Phospholipase A-2 (332)
 Phospholipase C (332)
 Triacylglycerol hydrolase (332)

Amines and amides (not placed in previous categories)

Acetamide derivatives (16)
 Acyclic amides (290)
N-Adamantyl *n*-alkanamides (408)
 Clofibrilic acid amides (321, 342)
N,N-Didodecyl acetamide (16)
 Di-2-ethylhexylamine (66)
 Diethyl methyl benzamide (39)
N,N-Diethyl-*m*-toluamide (68, 131-133, 218, 299, 326)
N,N-Dimethyl-*m*-toluamide (309)
 Ethomeen S12 [bis-(2-hydroxyethyl)oleylamine] (86, 87, 299, 346)
 Hexamethylene lauramide (95)
 Lauryl-amine (dodecylamine) (240, 299, 346)
 Octyl amide (233)
 Oleylamine (240)
 Unsaturated cyclic ureas (61, 62, 293, 299)
 Urea (43, 109, 172, 185, 256, 285, 299, 304, 346)

Complexing agents

β - and γ -cyclodextrin complexes (52, 53)
 Hydroxypropyl methylcellulose (Carbapol 934) (91, 100)
 Liposomes (113, 195)
 Naphthalene diamide diimide (398)
 Naphthalene diester diimide (398)

Macrocyclics

Macrocyclic lactones, ketones, and anhydrides (optimum ring-16) (114, 346)
 Unsaturated cyclic ureas (61, 62, 293, 299)

Classical surfactants

Brij 30 (201, 202)
 Brij 36T (207, 216, 307, 346)
 Brij 35 (204, 209)
 Brij 52 (207)
 Brij 56 (207, 208)
 Brij 58 (203, 207, 208)
 Brij 72 (208)

Brij 92 (209)
 Brij 96 (206, 207)
 Brij 98 (208)
 Cetyl trimethyl ammonium bromide (218, 299, 346)
 Empicol ML26/F (299)
 HCO-60 surfactant (59)
 Hydroxypolyethoxydodecane (99)
 Ionic surfactants (ROONa, ROSO₃Na, RNH₃Cl, R = 8-16) (79)
 Lauroyl sarcosine (334)
 Nonionic surface active agents (134)
 Nonoxynol (386)
 Octoxynol (386)
 Phenylsulfonate CA (299)
 Pluronic F68 (201, 207, 285)
 Pluronic F127 (285)
 Pluronic L62 (201, 207)
 Polyoleates (nonionic surfactants) (92, 135)
 Rewopal HV10 (207)
 Sodium laurate (346)
 Sodium lauryl sulfate (sodium dodecyl sulfate) (56, 59, 60, 126, 269, 295, 299, 335, 346)
 Sodium oleate (326, 335)
 Sorbitan dilaurate (388)
 Sorbitan dioleate (388)
 Sorbitan monolaurate (388)
 Sorbitan monooleates (48, 50, 346, 388)
 Sorbitan trilaurate (388)
 Sorbitan trioleate (388)
 Span 20 (134)
 Span 40 (201, 203)
 Span 85 (206)
 Synperonic NP (299)
 Triton X-100 (207)
 Tween 20 (32, 102, 134, 147)
 Tween 40 (201, 203)
 Tween 60 (147)
 Tween 80 (147, 170, 346, 396)
 Tween 85 (206)

Others

Aliphatic thiols (316)
 Alkyl *N,N*-dialkyl-substituted amino acetates (22)
 Anise oil (232)
 Anticholinergic agent pretreatment (149)
 Ascaridole (241, 299)
 Biphasic group derivatives (54)
 Bisabolol (299, 306, 339, 346)
 Cardamom oil (405)
 1-Carvone (382)
 Chenopodium (70% ascaridole) (241, 299)
 Chenopodium oil (232, 299)
 1,8 Cineole (eucalyptol) (83, 197, 234, 237, 241, 299, 326, 345, 346, 402)
 Cod liver oil (fatty acid extract) (236)
 4-Decyloxazolidin-2-one (297)
 Dicyclohexylmethylamine oxide (67)
 Diethyl hexadecylphosphonate (329)
 Diethyl hexadecylphosphoramidate (329)

Miscellaneous compounds and groups, continued

- 4, 4-Dimethyl-2-undecyl-2-oxazoline (7)
N-Dodecanoyl-L-amino acid methyl esters (410)
 1,3-Dioxacycloalkanes (SEPA) (346)
 Dithiothreitol (26)
 Eucalyptol (cineole) (83, 197, 234, 237, 241, 299, 326, 345, 346, 402)
 Eucalyptus oil (232, 299)
 Eugenol (383)
 Herbal extracts (337)
 Lactam *N*-acetic acid esters (407)
N-Hydroxyethylacetamide (299)
 2-Hydroxy-3-oleoyloxy-1-pyroglyutamylpropane (12)
 Menthol (115, 237, 253, 271, 299, 348, 349)
 Menthone (380)
 Morpholine derivatives (120)
N-Oxide (389)
 Nerolidol (402)
- Octyl- β -D-(thio)glucopyranosides (136, 277)
 Oxazolidinones (406)
 Piperazine derivatives (120)
 Polar lipids (123, 143)
 Polydimethylsiloxanes (338)
 Poly [2-(methylsulfinyl)ethyl acrylate] (145)
 Polyrotaxanes (400)
 Polyvinylbenzyltrimethylammonium chloride (257)
 Poly(*N*-vinyl-*N*-methyl acetamide) (145)
 Prodrugs (142, 151, 399)
 Saline (skin hydration) (160)
 Sodium pyroglutamate (299)
 Terpenes and azacyclo ring compounds (15, 127, 196, 215, 231, 237, 238, 241, 242, 249, 253, 270, 273, 299, 306, 345, 346, 395)
 Vitamin E (α -tocopherol) (255)
 Ylang-ylang oil (232, 299)

N-methyl pyrrolidone and related compounds

- N*-Cyclohexyl-2-pyrrolidone (250)
 1-Butyl-3-dodecyl-2-pyrrolidone (330)
 1,3-Dimethyl-2-imidazolinone (62, 184)
 1,5 Dimethyl-2-pyrrolidone (299, 309)
 4,4-Dimethyl-2-undecyl-2-oxazoline (7)
 1-Ethyl-2-pyrrolidone (299, 309)
 1-Hexyl-4-methyloxycarbonyl-2-pyrrolidone (331)
 1-Hexyl-2-pyrrolidone (324, 325, 346)
 1-(2-Hydroxyethyl)pyrrolidinone (3)
- 3-Hydroxy-*N*-methyl-2-pyrrolidinone (317)
 1-Isopropyl-2-undecyl-2-imidazoline (7)
 1-Lauryl-4-methyloxycarbonyl-2-pyrrolidone (331)
N-Methyl-2-pyrrolidone (110, 121–125, 218, 234, 247, 259, 265, 276, 283, 299–301, 309, 317, 324–326, 354, 381)
 Poly(*N*-vinylpyrrolidone) (145, 392)
 Pyroglutamic acid esters (156, 157, 360, 372, 373)
 2-Pyrrolidone (2-pyrrolidinone) (247, 264, 295, 299, 301, 309, 330)

Ionic compounds

- Ascorbate (26)
 "Amphoteric cations and anions" (25)
 Calcium thioglycolate (56, 346)
 Cetyl trimethyl ammonium bromide (218, 299)
 3,5-Diiodosalicylate sodium (15)
 Ionic surfactants (ROONa, ROSO₃Na, RNH₃Cl) (79)
 Lauroylcholine iodide (200)
 5-Methoxysalicylate sodium (15)
 Monoalkyl phosphates (378, 379)
 2-PAM chloride, 4-PAM chloride (derivatives of *N*-methyl picolinium chloride) (14)
 Sodium carboxylate (289)
 Sodium hyaluronate (39)
 Sodium lauryl sulfate (sodium dodecyl sulfate) (56, 59, 60, 126, 269, 295, 299, 335, 346)

Dimethyl sulfoxide and related compounds

- Cyclic sulfoxides (328)
 Decylmethyl sulfoxide (31, 46, 63–65, 118, 163, 191, 216, 227, 234, 250, 295, 299, 300, 302, 304, 305, 307–309, 311, 335, 346)
 Dimethyl sulfoxide (66, 72–74, 77, 78, 80, 81, 126, 138, 144, 170, 186, 191, 218, 249, 259–261, 263, 274, 285, 295, 299, 309, 311, 317, 323, 346)
 2-Hydroxyundecyl methyl sulfoxide (13)

Solvents and related compounds

Acetamide and derivatives (16)
 Acetone (263, 299)
n-Alkanes (chain length between 7 and 16) (239, 242, 298, 315)
 Alkanols, diols, short-chain fatty acids (18–21, 217, 230, 239, 299, 347, 381)
 Cyclohexyl-1,1-dimethylethanol (17)
 Dimethyl acetamide (71, 72, 218, 274, 275, 295, 299, 309)
 Dimethyl formamide (72, 75–82, 138, 144, 185, 191, 218, 246, 264, 274, 275, 285, 299, 309)
 Ethanol (17, 18, 32, 63, 83, 84, 213, 238, 252, 263, 275, 279, 283, 291, 295, 299, 309, 343, 350, 351)
 Ethanol/*d*-limonene combination (409)
 2-Ethyl-1,3-hexanediol (11, 346, 356–358)
 Ethoxydiglycol (transcutol) (374, 375)
 Glycerol (304)
 Glycols (24, 32, 77, 299, 346)
 Lauryl chloride (323)
 Limonene (291, 299, 346)
N-Methylformamide (299)
 2-Phenylethanol (411)
 3-Phenyl-1-propanol (411)
 3-Phenyl-2-propen-1-ol (411)
 Polyethylene glycol (74, 78, 80, 146, 170, 299)
 Polyoxyethylene sorbitan monoesters (147, 346)
 Polypropylene glycol 425 (230)
 Primary alcohols (tridecanol) (150)
 Procter & Gamble system: small polar solvent (1,2-propane diol, butanediol, C3-6 triols or their mixtures and a polar lipid compound selected from C16 or C18 monounsaturated alcohol, C16 or C18 branched saturated alcohol and their mixtures) (20, 336)
 Propylene glycol (20, 31–33, 46, 63, 68, 69, 74, 77, 88, 89, 91, 92, 97, 98, 101, 109, 117, 118, 123, 124, 130, 131, 135, 140, 141, 143, 147, 152–155, 170, 173, 174, 176, 212, 231, 243, 252, 261, 263, 275, 294, 295, 299, 304, 305, 308, 309, 346, 353, 377)
 Span 20 (134)
 Squalene (252)
 Triacetin (393)
 Trichloroethanol (168, 169)
 Trifluoroethanol (168, 169)
 Trimethylene glycol (32)
 Tween 20 (32, 102, 134, 147)
 Tween 80 (147, 170)
 Xylene (66)

Azone and related compounds (see Patents, references 361–371)

N-Acyl-hexahydro-2-oxo-1H-azepines (254)
N-Alkyl-dihydro-1,4-oxazepine-5,7-diones (254)
N-Alkylmorpholine-2,3-diones (254)
N-Alkylmorpholine-3,5-diones (254)
 Azacycloalkane derivatives (-ketone, -thione) (29, 30)
 Azacycloalkenone derivatives (127, 179)
 1-[2-(Decylthio)ethyl]azacyclopentan-2-one (HPE-101) (327, 340)
N-(2,2-Dihydroxyethyl)dodecylamine (314)
 1-Dodecanoylhexahydro-1-H-azepine (4)
 1-Dodecyl azacycloheptan-2-one (azone or laurocapram) (6, 31–50, 118, 141, 148, 167, 176, 180–184, 186–190, 198, 214, 218, 224, 225, 233–235, 244, 245, 247–249, 256, 259, 261, 266–268, 271, 272, 274, 275, 278, 281, 282, 286–288, 290, 292, 293, 295, 299, 305, 308, 309, 311, 314, 315, 318, 320, 322, 326, 327, 333, 359, 376, 381, 402)
N-Dodecyl diethanolamine (397)
N-Dodecyl-hexahydro-2-thio-1H-azepine (247)
N-Dodecyl-*N*-(2-methoxyethyl)acetamide (314, 397)
N-Dodecyl-*N*-(2-methoxyethyl)isobutyramide (397)
N-Dodecyl-piperidine-2-thione (247)
N-Dodecyl-2-piperidinone (247, 248, 268, 314, 397)
N-Dodecyl pyrrolidine-3,5-dione (254)
N-Dodecyl pyrrolidine-2-thione (247)
N-Dodecyl-2-pyrrolidone (247, 248, 267, 268, 299, 314, 324, 325, 331, 346, 397)
 1-Farnesylazacycloheptan-2-one (6, 127, 244)
 1-Farnesylazacyclopentan-2-one (6, 127)
 1-Geranylazacycloheptan-2-one (6, 127, 221–223, 226, 244)
 1-Geranylazacyclopentan-2-one (244)
 Hexahydro-2-oxo-azepine-1-acetic acid esters (254)
N-(2-Hydroxyethyl)-2-pyrrolidone (319)
 1-Laurylazacycloheptane (8)
 2-(1-Nonyl)-1,3-dioxolane (314, 390, 397)
 1-*N*-Octylazacyclopentan-2-one (9)
N-(1-Oxododecyl)-hexahydro-1H-azepine (247)
N-(1-Oxododecyl)-morpholines (247, 248)
 1-Oxohydrocarbyl-substituted azacyclohexanes (10)
N-(1-Oxotetradecyl)-hexahydro-2-oxo-1H-azepine (248)
N-(1-Thiododecyl)-morpholines (247)

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2. *Drug Permeation Enhancement: Theory and Applications*, D.S. Hsieh, Ed. (Dekker, New York, 1994).
3. V.P. Shah, C.C. Peck, and R.L. Williams, "Skin Penetration Enhancement: Clinical Pharmacological and Regulatory Considerations," *Pharmaceutical Technology*, 1997, 21(11), 40–48.

mizing the ionization state of the drug are not necessarily chemical skin penetration enhancers.

Also, many of these studies used *in vitro* permeation techniques completed on excised animal skin. Depending on the species used and the experimental design, the significant enhancement found *in vitro* may not translate into improved clinical delivery in humans. Thus, even though a compound is cited as a skin penetration enhancer, it is the responsibility of the formulator to critically evaluate the validity of this assessment.

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