DRUG DEVELOPMENT COMMUNICATIONS, 2(1), 43-62 (1976)

FORMULATION REQUIREMENTS OF TOPICAL DELIVERY SYSTEMS

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ABSTRACT

The formulation of topical medication bases must inevitably respond to restrictions imposed by a number of physical properties of the medication itself (solubility, pH stability, ionic activity, etc.) as well as to various auxiliary effects desired, such as skin permeability or non-permeability, resistance to wash-off or ease of wash-off, speed of release of the drug, etc. All such factors determine the "formulation environment" to be provided for the active ingredient, in which it must then be tested for shelf-life stability, pharmacologic activity and safety.

Once the basic requirements have been determined for the formulation, it becomes relatively simple to set a "formulation profile" for the product - whether it shall be an anhydrous ointment or W/O or O/W emulsion; whether encapsulation or other techniques are required to provide "timed release" of the active ingredient(s); the type of preservative required; to what degree side-effects of the drug can be altered by various formulation techniques; and whether the active ingredient's keratin substantivity

can (or should) be altered by modification of the base vehicle.

INTRODUCTION

One would assume that the requirements for ideal stability of a drug, and for its release from the vehicle to the skin, would dictate a certain uniformity in the design of vehicles for particular drugs. No topical drugs perform equally well from both high and low pH vehicles, anhydrous ointments, from both W/O and O/W emulsions or alcoholic tinctures. One would therefore expect each drug to be offered for use only in the vehicle best suited for its intended use.

U.S. HYDROCORTISONE TOPICAL PRODUCTS

Yet, a look through the 1974 PDR[1] shows much disparity in this respect in terms of in U.S. marketed topical hydrocortisone preparations. A total of 38 products containing hydrocortisone (HC) are listed, offered by 18 different pharmaceutical manufacturers. Since HC is normally applied only via topical administration, for the following discussion we have eliminated those U.S. products intended for miscellaneous other uses such as opthalmic and otic drops, tablets or enemas. That leaves thirty different hydrocortisone brands and dosage forms offered for (routine) topical application. Hydrocortisone is the sole medication in 12 of these 30 products, whereas it appears in combination with antibiotics, sulfur, coal tar, heparin or iodochlorhydroxyquin in the remaining 18. Vehicle types among the 30 topical hydrocortisone preparations were divided as follows:

- 2 - Tinctures (one of which is an aerosol)
- 3 - Petrolatum or other anhydrous oily base
- 3 - Sodium Lauryl sulfate emulsions of fatty alcohols and/or fatty acids
- 4 - Soap emulsions (usually TEA stearate)
- 6 - GMS or POE Stearate emulsions

4 - Mixed systems - GMS + lanolin absorption base, or GMS + lanolin + Polysorbate + Sorbitan M/S + POE-40 stearate.

8 - Miscellaneous (unspecified "greaseless emulsion") types

30 - Total

In regard to pH, 25 of the 30 topical hydrocortisone commercial preparations contain water; the remaining 5 are either tinctures or anhydrous greasy ointments; these latter are of course not amenable to pH measurements. In the 25 preparations which do contain water, the following pH ranges apply:

8 products claim acid pH

4 must be alkaline (soap emulsions)

7 appear more or less neutral

6 are "hard to tell" from the PDR information supplied

25 (Total)

Finally, urea or colloidal sulfur are also present in 3 of the 25 aqueous emulsion products, presumably as mild keratolytic agents to promote increased activity of the hydrocortisone.

We are left with several difficult choices in trying to explain these diametrically opposed variations in hydrocortisone vehicle formulations:

1) It is possible that they were originally formulated at different times, when varying expert views prevailed in re ideal parameters for hydrocortisone vehicles.

2) Perhaps some of these formulations were influenced by the requirements of other drugs used in conjunction with the HC in 18 of these 30 topicals. However, even if this is the case it should be recognized that HC may be much less active in such "compromise" vehicles.

3) The final (doleful) possibility is that at least some formulators of these products

simply didn't know what they were doing. Or worse yet, perhaps their company attempts to build a particular "marketing bias" into its products (such as the safety and simplicity of petrolatum as a base, or the value of "skin pH"as a product claim, resulting in marketing pressures on the laboratory staff.

GENERAL

Although it would appear "self-evident" that the base formulation of topical medications must be compatible in every respect with the requirements of active ingredients incorporated therein, laboratory workers are frequently surprised to discover base instabilities, diminution of drug activity, or other signs of incompatability due to incorrect initial decisions in formulating the vehicle.

Such workers perhaps did not "do their homework" before plunging ahead with actual laboratory development work. This is not to say that formulating topicals is entirely a routine matter once all parameters have been fully defined. There is still a considerable amount of art to turning out elegant-appearing preparations, with pleasing skin-feel and other properties normally considered to be "cosmetic" in nature.

As we are all well aware, there are always surprises waiting in regard to actual "delivered activity" from OTC and Rx topical preparations (in comparison to the amount of medication actually incorporated into the base). Conversely, the drug frequently can have gross effects on the carrier base: its solubility characteristics (will it partition between the two phases of an emulsion?); its pH effect on the carrier base; its ionic activity (which may adversely affect emulsion or gel bases) and the syneresis which may occur in even the simplest ointment bases. Emulsion instability or gel collapse may develop in stable bases hitherto used successfully for other active ingredients.

We are long past the day of "universal" ointment bases, supplied to the neighborhood pharmacist, into which he is casually instructed to levigate almost any medicament he wishes. Such procedures may once have sufficed for simple raw materials such as the mercurials or zinc oxide, but today, neither the practicing physician nor the average pharmacist has the expertise required to make decisions regarding which base should be used to deliver specific topical corticosteroids, antibiotics or antifungal agents to the skin in effective amounts. As Dr. Howard Maibach pointed out last may[2], only 1% of most topically applied corticosteroids is absorbed through the skin from today's "normal" delivery systems. This percentage certainly could be improved via added formulating expertise. Maibach himself believes that inclusion of 10% urea in the vehicle doubles the sorption of steroids, and that anhydrous ointment bases are frequently more effective steroid delivery systems than emulsions (as demonstrated via the vaso-constrictor assay procedure).

Variations in base carrier formulations may affect efficacy of the medication in unexpected ways: whether a carrier base is washable or water-resistant is the simplest initial matter to be considered. Perhaps the base itself contains ingredients which react with either the skin or the medicament, thereby changing the release rate of the drug, or blocking access to the skin, affecting the rate at which it is able to perform its intended function.

There are numerous examples of the effects of incorporating proteins in carrier bases: Swartz observed in 1963 [3] that solubilized protein concentrates have a residual beneficial effect on acne vulgaris in teenagers; Horokova et al[4] showed a 5X prolongation of local anesthesia effects from the concommitant use of collagen with 0.5% Procaine. Finally, Lorenzetti et al[5] showed that inclusion of proteins retard the epidermal penetration of PABA sunscreens from ethanolic vehicles (though it appears that almost any alcohol-soluble material interferes with PABA's efficacy!).

KERATIN SUBSTANTIVITY

The degree of keratin substantivity (of either the medication or the carrier base itself) can control the efficacy of various preparations as well as their irritation potential. Substantivity to keratin is governed both by chemical and physical considerations; it is a phenomenon generally known as sorption, or more specifically, as adsorption.

Keratin substantivity is frequently related to the chemical structure of durgs, dyes and other "active" ingredients: symmetrical ions are attracted less strongly than assymetrical ones; the surface activity of materials has considerable influence on the process; long lipophilic chains give rise to rapid sorption at room temperature; anions combine with the amine groups of keratin to form salts; large anions show greater affinity than small ones; adsorption of anions is entirely controlled by pH, concentration and the relative anion affinities of the components in a mixture. As the pH drops, strongly substantive ions are attracted even more strongly, whereas in mixtures, ions with lower affinity sometimes drop off completely. When dye solutions are acidified with hydrochloric acid, only the dye itself is sorbed by skin and hair keratin, even though HCl alone is readily sorbed by keratin, and in fact is routinely used for the titration of the residual amino acid content of keratin.

Cationic agents per se are highly substantive to keratin, but high m.w. anion/cation complexes (1:1 mole ratios) are even more substantive, provided that they have not been "solubilized" by excess amounts of either the anionic or cationic component of such complexes, or by extraneous nonionic surfactants. These substantivity effects are discussed in greater detail in several previous papers[6,7,8] by this author.

"Substantivity" effects are also suspected of being primarily responsible for the "anti-irritant" properties shown by certain ingredients used in cosmetics and topical pharmaceutical preparations. Certain additives reduce the skin and eye irritation of various caustic products without unduly reducing their efficacy as active ingredients. This is the crux of the definition of the term, anti-irritant. Simply reducing the concentration of products will (of course) proportionately reduce side effects (such as skin irritation), but reduction of efficacy also usually occurs via this approach. In contrast, true anti-irritants allow formulators to reduce undesirable side effects without paying that price.

Anti-irritants found useful for topical cosmetic preparations[9] include Polypropylene Glycol 2000, Miranol C2M, PVP (K-30) and Azulene for alcoholic preparations; dithioglycolic acid for proteolytic enzyme preparations; and Tween 20 or Myvacet 9-40 for aluminum salt antiperspirant sprays. Allantoin has been used as an anti-irritant in a variety of topical preparations, ranging from body powders to lipsticks containing "bromo acid" dyes (which occasionally cause cheilitis-type reactions). Recently, an imidazolidinyl urea antiseptic, Germall 115 has been reported[10] to display topical anti-irritant properties.

Substantivity to keratin can either enhance or reduce the efficacy of active ingredients; it may result in the agent being sorbed solely at the surface of the skin, therefore not penetrating at all. Whether this is "good" or "bad" evidently depends on the condition being treated and the effects desired by the prescribing physician. Skilled pharmaceutical formulators can frequently control this factor, but if not, they should at least recognize that it may exist for a particular active ingredient in certain carrier bases. Thus - we now see the occasional use of protein adjuvants, anion-cation complexes, or high

molecular weight oils to adjust the keratin substantivity of topical drug preparations.

Finally, certain "combination techniques" can occasionally produce rather spectacular "substantivity" effects. These techniques depend on the active ingredient having specific solubility characteristics - ideally it should be highly soluble in a particular solvent, and neither the drug nor the solvent should be particularly water soluble. The drug will tend to partition in such binary solvent-water mixtures, most of it dissolving in the minor (solvent) portion. When such binary solutions are applied to the skin, the solvent frequently "plates out" onto the skin, carrying with it a high load of active ingredient. By such means, nominal "1% solutions" of medication may (for all practical purposes) become 10% solutions, if that is the concentration of drug in the solvent "phase".

Certain lipophilic polyols, or alcohols (such as benzyl alcohol and phenyl ethanol) can serve this purpose. Both the drug and such solvents concentrate at the skin surface; thus permeation is also improved. The water solubility of solvents used for this purpose should be rather limited (2-5% seems ideal). Solubility characteristics of the drug itself can be altered to take deliberate advantage of such possibilities. Formula manipulation of this sort was discussed at some length in a paper published about 12 years ago[8] and the technique has been successfully used commercially to produce hair dyes with minimal concentrations of active ingredients.

There is also a reverse phenomenon to surface sorption: skin penetration with little systemic absorption was recently claimed for Schering's Lotrimin clotrimazole preparations. Successful treatment of deep-rooted Tinea and Candidiasis fungal infections is achieved when this drug penetrates the epidermis in concentrations inhibitory to susceptible fungi. Yet, there is apparently no detectable sorption into the bloodstream. This fortunate

state of affairs is presumably due to basic properties of the drug itself, not to any mysterious formulating techniques used in making up its commercial bases (1% in PEG 400, and 1% in a nonionic cream). As a matter of interest however, we should perhaps note that Lotrimin Cream contains 1% benzyl alcohol "as a preservative". The benzyl alcohol in that cream may act in more ways than suspected. It may "plate out" onto the skin.

GENERAL INFORMATION

Two other formulating techniques should perhaps be touched on:

1) Various methods exist for ensuring the "slow-release" of active ingredients from their carrier base. The use of soluble proteins in topical carrier bases has already been discussed. The major approach however, is the use of sophisticated encapsulation techniques. Microcapsules are generally formed via coacervation techniques, coating pharmaceuticals with gelatin, ethyl cellulose, or other film formers. Sometimes known as "spansules" and generally used primarily for oral preparations, such microcapsules offer unique possibilities in the formulation of ointments, creams, lotions and topical dressings for various topical uses[11].
2) A similar approach is the use of impregnated tapes - such as Cordran, the flurandrenolide transparent polyethylene tape offered by the Lilly's Dista Division.

Humectants vs Moisturizers:

It has been claimed that as little as 2% sorbitol will cut the moisture loss from O/W soap emulsions by 40%. This effect of sorbitol however is much less pronounced in nonionic emulsified creams and ointment bases.

The battle between various polyols for this purpose has raged for several decades and we shall not attempt to settle it today. Sorbitol, glycerine, propylene glycol

or the polyethylene glycols all fill one major function - preventing preparations from drying out and caking around the cap. This problem is especially prevalent in O/W emulsions carrying a heavy pigment load of zinc oxide, or other insoluble powders. The writer frequently prefers to use PEG 400 in such preparations for two reasons:

1. It provides greater slip (lubricity), thereby promoting spreading on the skin.
2. It is distirctly less irritating than propylene glycol, an important factor when using large percentages of polyol to form gels or solid stick bases.

However, polyols are not necessarily moisturizers for the skin. Despite the traditional use of Rosewater/glycerine and similar preparations to treat chapped skin, users are just as likely to end up dessicating their skin by such means rather than moistening it. Polyols are indiscriminate in obtaining moisture; our skin is merely a very thin covering over a vast reservoir of water, our bodies. If the relative humidity on a particular day is low, topical use of large percentages of polyols means that these compounds will simply satisfy their "need" to maintain a water-equilibrium by drawing moisture from the body, instead of attracting it to the skin surface from external sources.

In cosmetic industry usage, moisturizers are preparations containing only modest amounts of polyols. Instead they are mainly based on various "absorption base" materials, to which water has been added to form an emulsion. This approach sometimes can get quite sophisticated. There are many attempts to match natural sebum, which in fact does help regulate the moisture level of our skin. Syntex has such a mixture which it uses in topicals. Mixtures of various amino acids, lipoproteins, urea, ureides, squalene and lactic acid or pyrollidone carboxylic acid salts are offered under various trademarks. The phrase "NMF" (Natural Moisturizing Factor) is actually a trademark of the Kolmar Co., which sells one such mixture

developed by Dr. Otto Jacobi[12, 13] a number of years ago.

There's more to come: substantive polyols are being developed which are cationic; combinations of collagen protein with various fatty materials and/or lanolin are also now available. A whole new world is opening up as both cosmetic and OTC pharmaceutical manufacturers attempt to ride the booming "moisture market".

Skin Feel:

We often mouthe generalities such as, "W/O emulsions feel greasy while O/W ointment bases do not." Although it is true that O/W emulsions disperse in water and are therefore easier to remove from the skin, nevertheless, the skin feel of all topical formulations is exquisitely controllable. Here is where the "art" of the formulator comes into play. You can add certain esters to greasy mineral oil/petrolatum mixtures and greatly reduce their oily feel. If you then add fatty alcohols, the skin feel is transformed to a rich, dry-velvety effect. Finally, if you add PEG 400 to the water phase (or certain slippery gums) that dry velvetiness can be transformed to a moist (lubricant) feel. Further changes in skin feel are clearly discernible as you switch to branched chain esters or alcohols, from non-polar to more polar esters, to certain isomers or cationic additives. All of this is routine stuff for the cosmetic chemist. Primarily interested in skin feel, he has even begun to quantitate various cosmetic emollients in this respect[14]. It behooves the pharmaceutical formulator to be aware of the many such possibilities which exist for improving the elegance of his preparations. That very elegance can someday spell commercial success, if it turns out to be the primary difference between his and a competitor's product.

In closing, I should mention two new types of raw materials which should be of interest to ointment base formulators:

1) The first are those oleic and stearic diethanolamides which are oil soluble, in contrast to the water soluble coconut fatty acid amides used in most shampoo work. These amides form stable W/O emulsions at ambient temperatures. One use for them has been to form water-in-propellant aerosol emulsions in situ, (right in the can), as a means of reducing corrosion.
2) The amine oxides (such as the C_{18} dimethyl amine oxide) can replace polysorbates and the sorbitan esters at much lower surfactant concentration levels. Furthermore, they do not exhibit "nonionic interference" with preservatives.

ILLUSTRATIVE FORMULATIONS

I. ANHYDROUS BASES:

The simplest anhydrous base, of course, is petrolatum, either alone or in combination with mineral oil. Adding a surfactant converts this system to an absorption base:

90.0	Petrolatum
10.0	sorbitan sesquioleate (W/O emulsifier)

This mixture will hold water, either when added deliberately to form a rather crude emulsion, or by absorbing moisture directly from the skin. The above formulation will hold up to approximately 40% water.

Hydrophilic Petrolatum USP is essentially a lanolin absorption base, containing cholesterol as the W/O emulsifier, with stearyl alcohol and beeswax added to control viscosity and stabilize subsequent emulsions made by adding water to it.

Hydrophilic Ointment USP is another water absorption base type, although the water

(30%) has now been added. The petrolatum is down to 25% in this product with stearyl alcohol again added for viscosity control and 12% propylene glycol as a solvent/preservative. The emulsifier in this case is 1% sodium lauryl sulfate.

USP Coal Tar Ointment is petrolatum based, with approximately 25% ZnO and 25% starch to help hold (and camouflage) the 1% coal tar content. An O/W emulsifier is used in this anhydrous ointment, 0.5% Polysorbate 80.

Bath Oils, both the floating and dispersible types are excellent vehicles for applying medication evenly and quickly over the entire body. The floating types are generally based on 60-80% mineral oil, about 20% fatty ester or unsaturated natural oils such as mink or sesame, plus a spreading agent such as lanolin alcohols or the PPG 20 lanolin ether. Dispersible bath oils may have the same oil content, plus the use of about 10% PEG400 dioleate as the dispersant.

II. WATER-IN-OIL OINTMENT BASES

Pure Nonionic form		Nonionic/Lanolin Type	
28.0	Petrolatum	33.0	Mineral Oil
2.0	Sorbitan Sesquioleate	10.0	Microcrystalline wax
1.0	Polysorbate 80	5.0	Cetyl Alcohol
69.0	water	2.0	Lanolin alcohol
		3.0	Sorbitan Sesquioleate
		3.0	Glycerine
		44.0	water

The pure nonionic formula above (left) is based on a combination of both W/O and O/W emulsifiers, allowing the use of much lower emulsifier levels

and producing more stable emulsions. In the combination Nonionic/Lanolin formulation above (right) both the lanolin alcohol and the sorbitan sesquioleate are powerful W/O emulsifiers (low HLB). The cetyl alcohol and microcrystalline wax serve to control viscosity and set up a crystalline structure in the final cream, which provides shelf-life stability.

W/O Zinc Oxide Base

7.5	Hydroxylated Lanolin
23.0	Petrolatum
12.0	Mineral Oil (70 visc)
2.0	Silicone Fluid 200 (350 cts)
3.5	Ozokerite wax
24.0	Zinc Oxide
2.0	Sorbitol, 70%
25.0	Water

The hydroxylated lanolin is a primary W/O emulsifier which also aids in dispersing the Zinc Oxide. Further, it is an excellent emollient and moisturizer for this product intended for baby diaper areas. The silicone and ZnO together are powerful water repellents.

III. OIL-IN-WATER EMULSIONS

High PEG Content Cream	Basic O/W System
15.0 Emulsifying Wax NF	5.0 Coceth 6
12.0 Oleyl Alcohol	25.0 Mineral oil
6.0 Ethoxylated Lanolin	70.0 water
28.0 PEG 4000	
39.0 Water	

The basic emulsifiers in both the above formulas are quite similar. Both Emulsifying Wax NF and Coceth 6 are mixtures of cetyl and stearyl alcohols to which ethoxylated cetyl/stearyl alcohols have been added. The Emulsifying Wax NF also has a rather high ester content however, which limits its uses to medium pH ranges; Coceth 6 can be used from pH 2.5-11.5.

"Mayonaise Type Emulsion	Non-oil O/W Emulsion
85.0 Cottonseed Oil	5-10 cetyl/stearyl alcohols
0.5 Polysorbate 80	5.0 Glyceryl Monostearate (Acid Stable SE type)
14.5 Water	5.0 Sorbitol, 70%
	80-85 water

The "Mayonaise Type" is a true O/W emulsion, with only 14.5% water as the outer (continuous) phase. It feels oily, yet is dilutable with water. Its high viscosity helps maintain emulsion stability. The Non-oil type above (right) contains no mineral oil, no esters, no liquid fats of any sort. This type of approach can be used for so-called "roll-up" preparations, where paraffin is frequently used rather than the fatty alcohols above.

IODOPHOR CREAM

Phase A:		
	12.0	Glyceryl Monostearate (nonionic SE)
	2.5	Coceth 6
	6.0	Ethyl hexyl palmitate
	4.0	Mineral oil
Phase B:		
	49.5	Water
	5.0	Propylene Glycol
Phase C:		
	20.0	Water
	1.0	Nonoxynol-9 (20% Iodine)
	100.0%	

This cream contains 0.2% free iodine. It could tolerate somewhat more, but to go to significantly higher levels would require use of a different iodine complex. This one is surface active and reduces emulsion stability.

O/W UREA CREAM

Phase A:		
	10.5	Mink Oil
	8.0	Glyceryl Monostearate (pure)
	3.0	Ceteareth-15
	2.3	Coceth 6
Phase B:		
	10.0	Carbamide
	4.5	PEG 400
	61.7	Water
	100.0%	

Carbamide has always been difficult to incorporate into emulsions because it tends to complex certain straight-chain oily compounds, and acts as a solubilizer for others, thus promoting partitioning of ingredients between emulsion phases. Further, it can hydrolyze, leading to pH drift. This formulation is an extraordinary skin softener, using mink oil (75% unsaturated triglycerides) in the fat phase and 10% urea in the aqueous phase. A stable, purely non-ionic formulation.

CLEAR GEL ALCOHOLIC BASE

Phase A:		
	0.70	Carbomer 940
	56.15	Water
Phase B:		
	4.0	PEG 400
	35.00	Ethanol (95% SDA 40)
	0.55	Isopropanolamine
	3.00	Nonoxynol-15
	0.10	Menthol
	0.50	Active (antiseptic, sulfur, etc.)
	100.00%	

Based on the familiar Carbomer system, neutralized with isopropanolamine, this formula uses an ethoxylated nonyl phenoxy compound (Nonoxynol-15) as solubilizer for whatever small amounts of oil or active ingredients which

need to be incorporated into this crystal clear base. Similar type gels can be produced using cellulose gums.

EXPANDING FOAM BASE

Phase A:		
	3.40	PEG 20 Stearate
	0.15	Diethanolamine
	4.50	Mineral oil
Phase B:		
	0.20	Carbomer-941
	67.75	Water
Phase C:		
	24.00	Propellent 12/114 (10-90%)
	100.00%	

This type of formulation is of interest for vaginal contraceptives and similar uses. The heavy mineral oil acts as an anti-irritant.

COLLAPSIBLE FOAM

Phase A:		
	2.4	PEG 20 Stearate
	1.0	Lanolin alcohols
	2.0	F.A. ester (IPM, lactate, etc.)
	1.0	Myristyl Myristate
	3.8	Mineral Oil
Phase B:		
	65.8	Water
Phase C:		
	12.0	Ethanol (95% SDA 40)
Phase D:		
	12.0	Propellent 12/114 (40-60%)
	100.0%	

Collapsible foams, in contrast to the "Quick Break" type, will hold as a rich foam until actually rubbed on the skin where the combination of body heat and pressure will cause them to collapse. The ethanol content controls the speed and ease with which such foams collapse.

CROSS-INDEX TO SPECIAL INGREDIENTS USED IN FORMULAS

Formula Ingredient Designation	Trade Name (Supplier)
Ceteareth-15	Lipocol SC-15 (Lipo Chemical)
Coceth 6	Promulgen D (Robinson Wagner)
Emollient Oils	Avocado, mink or sesame oils
Emulsifying Wax NF	Polawax (Croda Ltd.)
Ethoxylated Lanolin	Solan (Croda Ltd.)
Ethylhexyl Palmitate	Ceraphyl 368 (Van Dyk & Co.)
Glyceryl monooleate	(Armak Div.)
Glyceryl monostearate, nonionic SE	Cerasynt 945 (Van Dyk & Co.)
Glyceryl monostearate, acid stable SE	Arlacel 165 (Atlas/ICI)
Hydroxylated Lanolin	OHlan (Amerchol/CPC)
Lanolin Alcohols	Ritachol (R.I.T.A), Ceralan Robinson Wagner), Super Hartolan (Croda Ltd.)
Mink Oil	Emulan (Emlin Inc.)
Myristyl myristate	Ceraphyl 424 (Van Dyk & Co.)
Nonoxynol-9 iodide	Biopal VRO-20 (GAF Corp.)
Nonoxynol 15	Igepal CO 730 (GAF Corp.)
PEG 400	Carbowax 400 (Union Carbide)
PEG 4000	Carbowax 4000 (Union Carbide)
PEG 400 dioleate	Emulsynt 600 (Van Dyk & Co.)
PEG 20 stearate	Cerasynt 840 (Van Dyk & Co.)
Polyoxyl 40 Stearate	USP
Polysorbate 80	Tween 80 (Atlas/ICI)
Silicone Fluid 200 (350)	(Dow Corning)
Sorbitan Sesquioleate	Arlacel 83 (Atlas/ICI)
Sorbitol 70%	Sorbo 70 (Atlas/ICI)

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