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Topical drug classification☆

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Abstract

Current definitions of lotions, gels, creams and ointments vary depending on literature source, market history or traditional use. This often leads to confusion when deciding which dosage form to prescribe and/or purchase. The existing classification of topical dosage forms needs to be re-examined to ensure that definitions for different dosage forms are based on consistent scientific principles and that dosage forms can be distinguished from one another. The purpose of this study is to obtain a scientifically based, systematic classification of dosage forms for topical drugs.

A variety of prescription and over-the-counter topical products currently marketed as lotions, gels, creams, and ointments are evaluated using different techniques including rheology (viscosity and shear rate versus shear stress), loss on drying (LOD), specific gravity, surface tension, thermogravimetric analysis (TGA), water absorption, dilution properties, microscopic evaluation, transmittance of visible light, appearance and composition. Rheology is the most discriminating property separating creams and lotions. Water plus volatiles (as measured by LOD) and composition separate ointments and creams. Composition and thermal behavior separate gels from the other dosage forms. Based on these findings, new definitions and a decision tree are presented to assist in the determination of the appropriate nomenclature for a topical dosage form.

Keywords: Ointment; Cream; Gel; Lotion; Topical drug

☆ This scientific contribution is intended to support regulatory policy development. The views presented in this article have not been adopted as regulatory policies by the Food and Drug Administration at this time.

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1. Introduction

The classification of topical dosage forms has not been based on any scientific definition. Current definitions of lotions, gels, creams and ointments vary depending on literature source, market history or traditional use. Some of these dosage form terms are ill defined and not very concise. The current Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) Data Standards Manual defines ointment as "a semisolid preparation intended for external application to the skin or mucous membranes", cream as "a semisolid dosage form containing one or more drug substances dissolved or dispersed in a suitable base. . ." and lotion as ". . .topical suspensions, solutions and emulsions intended for application to the skin." (See CDER Data Standards Manual at http://www.fda.gov/cder/dsm/DRG/drg00201.htm (January 2005), CDER approval date 14 April 1992) These definitions do not differentiate between the three dosage forms (i.e., ointment, cream and lotion). The United States Pharmacopeia (USP) definitions for ointments and creams are essentially the same as the definitions the FDA uses. The USP does not define lotions; instead, one is referred to solutions or suspensions (See USP 28 ⟨1151⟩ Pharmaceutical Dosage Forms; *USP 28*, The United States Pharmacopeial Convention: Rockville, MD, 2005. 2701–2712). The British Pharmacopoeia (BP) defines lotions as liquids, but does not clearly differentiate between lotions and other liquids such as suspensions and solutions (See BP 2004, "Liquids for Cutaneous Application of the British Pharmacopoeia"). The Japanese Pharmacopoeia (JP) includes creams with the ointment definition, and the European Pharmacopoeia defines ointments as single-phase and creams as multiphase systems (See JP, December 2001, "General Rules for Preparations" and EP 01/2005:0132, "Semi-solid Preparations for Cutaneous Application".)

These ambiguities can cause confusion for drug developers and regulators when deciding on the nomenclature for topical dosage forms as well as determining market exclusivity. Can one formulation be marketed as both a cream and a lotion? Can a light scattering material be added to a gel to create a formulation that can now be marketed as a cream or lotion? Physicians have certain expectations when prescribing a certain dosage form. Lotions and creams are expected to be easy to apply and remove (water washable) and can leave a cooling sensation on the skin. Ointments are usually more difficult to apply or remove, but are expected to act as a barrier and increase the hydration of the skin.

The purpose of this study is to establish a scientific basis for a systematic, coherent and meaningful classification of dosage forms for topical drugs. Such a classification will allow physicians to use the dosage form as a guide to the desired properties that may be critical in prescribing topical drugs for a patient. Subjective tests like feel and appearance are often used to describe topical dosage forms. This study strives to replace these observations with more precise analytical measurements that can be used as a basis to define these dosage forms. Definitions will be consistent with the subjective expectations of patients and physicians when prescribing a topical product (e.g. ease of application and removal, feel of the product on the skin, barrier properties, etc.)

In this study, topical drugs refer to those drugs administered to a spot on the outer surface of the body (dermatological applications). Drugs meant for other topical application (e.g. oral, nasal, aural, vaginal, and rectal areas) are not included in this study. However, the proposed definitions may be utilized in the future for these alternative applications. Dosage forms tested are limited to solutions, lotions, gels, creams and ointments. Revised definitions are proposed for topical solution, topical suspension, lotion, gel, cream, ointment and paste.

The vehicle plays a key role in the appearance, feel, and successful application of a topical drug (Barry, 1983). Therefore, the composition of a topical drug vehicle should be considered in its nomenclature. However, composition alone cannot be used to define a dosage form since one ingredient can have multiple functions (e.g. poloxamer functions as a suspending agent, gelling agent, thickening agent, emulsifier and/or wetting agent), and the manufacturing process can change product properties. In determining what additional properties should be used to define a dosage form, the following physical properties were studied in 58 topical products: rheology (viscosity and shear rate versus shear stress), loss on drying (LOD, a measure of water and volatiles), specific gravity, surface tension, thermogravimetric analysis (TGA), water absorption, dilution properties, microscopic evaluation and transmittance of visible light. The more subjective proper-

ties (e.g. appearance and feel) were used to evaluate products that had properties bordering between two dosage forms.

2. Materials and methods

2.1. Preparation of samples

Twenty over-the-counter and 33 prescription topical products were obtained from drug manufacturers and local drug stores. Over-the-counter products with similar uses were chosen off the shelf of a local drug store. Criteria for including a prescription drug in this study include: approval since 1997, available in different dosage forms or multiple manufacturers, or containing a drug base that borders between two dosage forms. Three USP ointment bases were prepared: white ointment, polyethylene glycol ointment and hydrophilic ointment (see Hydrophilic Ointment, White Ointment and Polyethylene Glycol Ointment; *USP 28*, pp.1415 and 3055). Two gels were prepared following procedures from literature: mineral oil gel and zinc oxide gel base (Lieberman et al., 1996b). Products are listed in Table 1. All products were tested as they would be applied by a consumer (i.e., mixing or shaking before use only if called for in the labeling).

2.1.1. Composition

The composition of over-the-counter products was determined from the labeling. For prescription products, drug applications submitted to the FDA were consulted for the amounts and types of ingredients.

2.1.2. Rheology

For viscosity, samples were incubated at 25 °C for at least 16 h in a VWR Model 2005 incubator and then run on a Brookfield DV-II+, Model RV with Wingather software viscometer at 5 rpm and 25 °C. Spindles were chosen to maintain a torque between 10% and 90%. The RV spindles gave viscosity at a single immersion point in the sample. The Helipath T-Bar spindles were rotated down and up in the sample, giving viscosity at a number of points programmed over the run time. Five readings taken over a period of 60 s were averaged to obtain the viscosity. The viscometer was calibrated using Brookfield viscosity standard 5000 (100% polydimethylsiloxane). Shear-rate versus shear-stress plots were obtained using the small sample adapter of the above Brookfield viscometer. General trends of the rheology were confirmed using a Thermo/Haake Visco Tester 7L with a L4 spindle by placing the sample in a 13 mm × 100 mm test tube. The RPM of the spindle was adjusted over a range of values, and the apparent viscosity recorded. The Thermo/Haake Viscometer is limited in its ability to measure high viscosity, thus not all products tested had the same number of readings.

2.1.3. Loss on drying (LOD)

%Water and volatiles were measured by loss on drying. Approximately 3 g of the sample were dried at 105 °C for 24 h and then to constant weight.

2.1.4. Specific gravity

Specific gravity was determined by comparing the net weight of a sample with the net weight of deionized water using a Fisher Pycnometer (Catalog No. 03-247).

2.1.5. Surface tension

This test was performed by Dun Chen, Ph.D., of CYS Company using a Thermo Cahn DCA 322 system. A small platinum strip (2.3 mm in width) was used as the solid probe. This probe was immersed 2 mm into the sample and then pulled to the surface at which position the surface tension information was collected as a function of time. Surface tension values were decided by the achievement of a stable value or after 2 min of data collection. Five runs were made on each sample.

2.1.6. Thermogravimetric analysis (TGA)

TGA measurement was done in a platinum pan at 10 °C/min to 500 °C (blank curve corrected) with an atmosphere of 50 mL/min nitrogen. The equipment was a Shimadzu TGA-50.

2.1.7. Visible transmittance

The sample was placed in a 0.1 mm demountable cell and scanned from 400 to 700 nm in an Agilent 8453 spectrophotometer. Mean percent transmission and absorbance were determined by averaging the % transmission and absorbance at six visible wavelengths (410, 450, 500, 550, 600, and 650 nm).

2.1.8. Visual appearance and feel

Several subjective tests were used to evaluate the appearance of the products. A drop of the sample was

Table 1
Topical products evaluated in this study

Topical products	Lotion	Cream	Gel	Ointment
Over-the-counter (OTC)	Banana boat cool colors vanishing sunblock, SPF 30	BENGAY pain relieving cream[a]	BENGAY pain relieving gel	Cortizone 10
	Coppertone sunblock lotion[a]	Clinique water dissolve cream cleanser	Coppertone sunblock gel	
	Neutrogena healthy skin face lotion (2 lots)	Cortaid cream[a]		
	Ombrelle lotion, SPF 40	Eucerin original moisturizing cream		
	Ombrelle lotion for kids SPF 44	Neutrogena deep clean cream cleanser		
	Vaseline intensive care lotion	Noxzema cleansing cream		
		Ponds cold cream (3 lots)		
		Vaseline petroleum jelly cream		
Prescription	MetroLotion (metronidazole 0.75%)	Carac cream (fluorouracil 0.5%)	BenzaClin topical gel (clindamycin 1%, benzoyl peroxide 5%)	Elocon ointment (mometasone furoate 0.1%)
	One product submitted for approval	Elocon cream (mometasone furoate 0.1%)	Duac topical gel (clindamycin 1%, benzoyl peroxide 5%)	Mometasone furoate 0.1% (Clay-Park)
		Ferndale hydrocortisone acetate (HCA) cream, 2.5%	Finacea gel (azelaic acid 15%)	Taro (CP) ointment
		Ferndale HCA lipocream, 2%	MetroGel (metronidazole 0.75%)	Temovate (CP) ointment
		Ferndale HCA lipocream, 2.5%	Solaraze gel (diclofenac sodium 3%)	
		Finevin cream (azelaic acid 20%)	Taro (CP) gel	
		MetroCream (metronidazole 0.75%)	Temovate (CP) gel	
		Metvix cream (methyl aminolevulinate)		
		Renova cream (tretinoin 0.02%)		
		Taro cream (clobetasol propionate (CP)) (two lots)		
		Taro cream (CP) emollient (two lots)		
		Tazorac cream (tazarotene 0.05%)		
		Temovate (CP) cream		
		Temovate (CP) emollient cream		
		Tri-Luma cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)		
		Three products submitted for approval		
Lab prepared			Base mineral oil gel	Hydrophilic ointment USP
			Zinc oxide gel base	Polyethylene glycol ointment USP
				White ointment USP
Totals	9	30	11	8

[a] Coppertone, BENGAY and Cortizone products were not included in the original multivariate analysis of lotion and cream products; they were obtained at a later time for comparisons with gels and ointments.

placed on a flat counter and the fate of the resulting drop recorded as a visual of indication of the rheology (thick or thin). A small amount of the sample was placed in a 5 mL beaker and the ability of the material to conform to the shape of the vessel recorded. Color and opacity were recorded. A panel of chemists, pharmacists and physicians examined those products whose physical characteristics seemed at odds with the dosage form on the label. The majority of the panel gave their view on what the dosage form should be based on the characteristics and visual appearance and feel of the product.

2.1.9. Microscopic examination

A Zeiss Polarizing Microscope, Model GFL at 400× magnification was used to examine samples for uniformity of particles and number of phases.

2.1.10. Dilution with water

Approximately 0.2 g of sample was placed in separate 50 mL flasks. About 50 mL of water was added and each flask shaken thoroughly. Each sample was observed for the effects of water dilution.

2.1.11. High humidity exposure

A humidity chamber was assembled using a sealed glass desiccator containing saturated ammonium phosphate monobasic solution. Relative humidity inside the chamber read at 96% using a digital hygrometer. Three grams of the topical product were weighed into a porcelain dish at ambient humidity of 30% RH. The dish plus sample was then placed into the humidity chamber. The chamber was sealed and the sample plus dish sat for 20 h at ambient temperature. After 20 h the humidified sample weight was compared to the initial sample weight at ambient humidity.

2.1.12. Multivariate analysis

Principle component analysis (PCA) is a mathematical technique that ranks the contribution of each measured variable to the overall variance among a group of samples. The first principle component accounts for the largest contribution to the collective variance among a group of samples and hence represents the best means to distinguish one class from another. An initial comparison of lotions and creams was done with the over-the-counter products by performing a PCA with measurements for viscosity, specific gravity, LOD and surface tension using Pirouette software version 3.02. The values were preprocessed by mean centering.

3. Results

3.1. Rheology, specific gravity, % water plus volatiles (by LOD) and surface tension

Literature sources list lotions as liquids and refer to creams as semisolids (Nairn, 2000; http://pharmlabs.unc.edu/emulsions/text.htm (January 2005)). Multivariate analysis of fourteen over-the-counter lotions and creams (see Table 1) using viscosity, surface tension, specific gravity and % water plus volatiles found that viscosity accounts for most of the variance between samples. The PCA verified that viscosity is the dominant factor and that specific gravity, % water plus volatiles and surface tension do not lead to a means of distinguishing between lotions and creams. Based on these findings, subsequent comparisons of the prescription lotions and creams did not include the variables of specific gravity, % water plus volatiles or surface tension.

Since viscosity is measured at only one shear rate, different types of materials (Newtonian, pseudoplastic, plastic) can have the same viscosity. A wider range of shear rate values was studied for lotions, creams, and gels, all with viscosities below 50,000 cP, to establish criteria to separate liquid from semisolid dosage forms. Plots of shear rate versus shear stress were correlated with observations of pourability of the dosage form and their conformability to containers at room temperature. Results show that liquids display Newtonian or pseudoplastic flow behavior with little or no force necessary to initiate flow. Semisolids are not pourable; they do not flow or conform to the shape of their containers at room temperature. They do not flow at low shear stress and generally exhibit plastic flow behavior. Fig. 1 (Brookfield data) and Fig. 2 (Thermo/Haake data) show examples of flow behavior for six over-the-counter or prescription lotions, creams, and gels. Higher shear rates are missing on the plots for the semisolids because of equipment limitations. It is evident that Finacea Gel, Clinique Cream, and BENGAY Gel exhibit semisolid behavior; while Banana Boat Sunblock, Coppertone Sunblock Gel, and Coppertone Sunblock Lotion display liquid behavior.

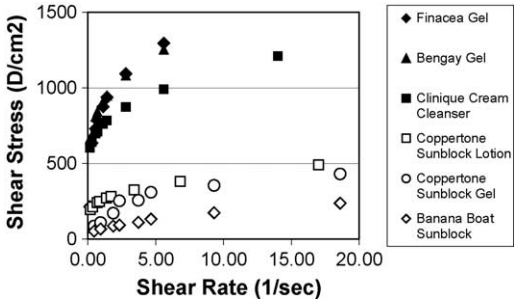

Fig. 1. Brookfield rheology data: shear stress vs. shear rate for six products. The three samples with closed symbols are semisolid (they are not pourable and do not flow at low shear stress conditions); the three samples with open symbols exhibit liquid behavior (i.e., pourable, conforming to container).

Viscosity data were also collected for 30 over-the-counter and prescription creams and ointments. Trend analysis indicates that ointments tend to be more viscous than creams; however, there is an overlap of several hundred thousand cP between creams and ointments. Because of this large overlap, no further rheology data were collected and no rheological criteria between creams and ointments were established.

As mentioned above, % water plus volatiles (by LOD) was not found to be a characteristic that could be used to separate creams and lotions; however, it was a discriminating property for some topical dosage forms. Generally ointments were found to have <20% water plus volatiles, and all lotions were found to have >50% water plus volatiles (see Fig. 3). Most gels were also found to have a high water and volatiles content.

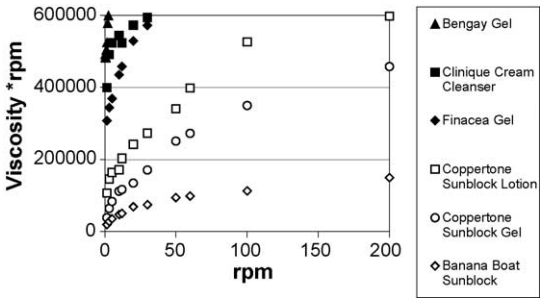

Fig. 2. Thermo/Haake rheology data: viscosity (cP) × rpm (proportional to shear stress) vs. rpm (proportional to shear rate) for same six products as in Fig. 1. Confirmation of flow behavior for liquid (open symbols) and semisolid (closed symbols) samples. As with the Brookfield instrumentation (Fig. 1) flow does not occur at low shear stress for semisolids.

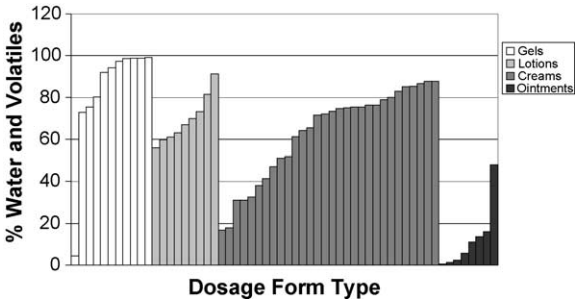

Fig. 3. % Water and volatiles (as measured by loss on drying) for 58 (over-the-counter, prescription and laboratory produced) topical products in four dosage forms. % Water and volatiles is found to be >50% for lotions and <20% for all but one ointment. The one ointment with >20% water and volatiles is the USP hydrophilic ointment found to have the look and feel of a cream.

The mineral oil gel was found to have a low water and volatiles content, and the USP Hydrophilic Ointment was found to be the only ointment to have >20% water and volatiles. A panel of pharmacists, chemists, and physicians examined the mineral oil gel and found the appearance and feel to be like that of an ointment. The panel found the look and feel of the USP Hydrophilic Ointment to be more like a cream than an ointment. This USP base is described in the literature as a water-removable base, which resembles a cream in appearance (Ansel et al., 1999). Water plus volatiles content is inversely proportional to the hydrocarbon and polyethylene glycol (PEG) composition of the topical product; see Fig. 4 for composition versus % water and volatiles for 25 prescription cream and ointment topical products and the ointments manufactured in the laboratory. Ointments, which are usually hydrocarbon or PEG based, have the lowest level of water and volatiles, and creams and lotions, which tend to be water based, have the highest levels. In general, ointments have a hydrocarbon or polyethylene glycol content greater than 50%. The only ointment not in the cluster at the top left of Fig. 4 is the USP Hydrophilic Ointment, which has a 25% hydrocarbon content and 50% water and volatiles content, and is the same ointment that was considered a cream by appearance and feel.

3.2. Thermogravimetric analysis (TGA)

TGA has been used to characterize topical dosage forms (Nesseem, 2001; Peramal et al., 1997; Kallioinen

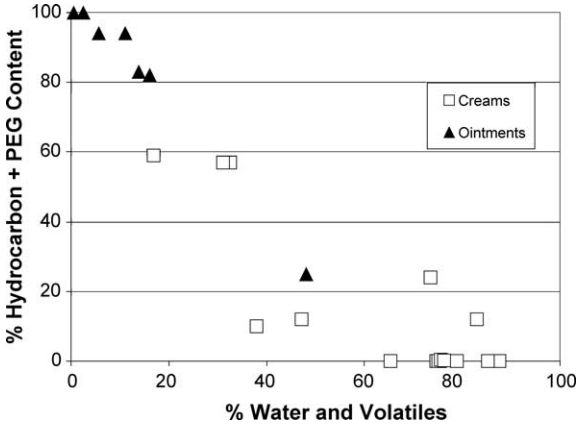

Fig. 4. % Hydrocarbon and polyethylene glycol (PEG) vs. % water and volatiles for 25 Prescription and Laboratory Prepared Creams and Ointments. % Water and volatiles is inversely related to the hydrocarbon and polyethylene glycol (PEG) content of the topical product. The one ointment with low % hydrocarbon + PEG content is the USP hydrophilic ointment whose look and feel was deemed to be more like a cream than ointment.

et al., 1995). Clear differences in the TGA curves of creams and gels were observed in this study. TGA curves show loss of free and bound water loss as well as loss of other volatiles. Gels, which tend to have aqueous or alcoholic vehicles containing a gelling agent that imparts a three dimensional structure, have one transition corresponding to the vehicle; whereas, creams, which tend to be multi-component emulsions, show multiple transitions corresponding to loss of free water, bound water and loss of other components (such as emulsifying agents, stabilizers, etc.) Figs. 5 and 6 give examples of the TGA curves for two drugs (clobetasol propionate and metronidazole) that are available in multiple dosage forms.

3.3. Transmittance

Clear or translucent gels are preferred by consumers (Lieberman et al., 1996a); however, many of the gels examined in this study were opaque. Table 2 lists 11 gels tested for % transmittance and absorbance, along with the appearance observed by the analyst. Six gels found to be clear had a transmittance greater than 85%. The remaining five gels were opaque and had a transmittance lower than 30%.

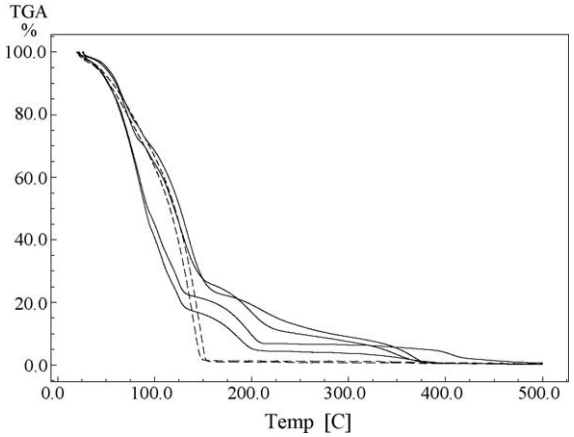

Fig. 5. Thermogravimetric curves for six clobetasol propionate products. The four products marketed as creams (solid lines) have multiple transitions; and those two marketed as gels (dashed lines) have one transition corresponding to the boiling point of the vehicle.

3.4. Microscopic examination

This evaluation was undertaken to determine if the emulsion and/or gel structure of topical dosage forms could be detected under microscopic examination. Many products showed two or more phases. For topical products where the active ingredient was crystalline, drug crystals could be seen. At 400× magnification, no structure in the clear gels was seen. Although many structural features were seen, no trends useful in distinguishing dosage forms were observed by this technique.

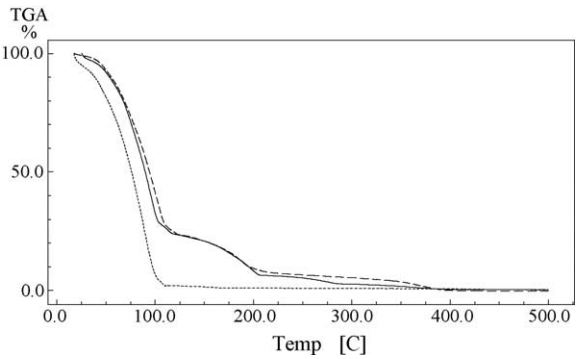

Fig. 6. Thermogravimetric curves for three dosage forms of metronidazole. The cream (solid line) and lotion (dashed line) have multiple transitions caused by the multi-component emulsion vehicles, and the gel (dotted line) has one transition corresponding to the boiling point of the vehicle.

Table 2
Appearance, % transmittance and absorbance of gel samples

Gel sample	Appearance	Mean % transmittance	Mean absorbance
MetroGel	Clear	93.4	0.030
Zinc oxide gel base	Clear	93.1	0.031
Taro clobetasol propionate gel	Clear	92.9	0.032
Temovate gel	Clear	91.2	0.040
Solaraze gel	Clear yellow	90.5	0.044
Coppertone sunblock gel	Clear yellow	88.8	0.053
Mineral oil gel	Opaque	28.5	0.56
Duac topical gel	Opaque white	22.6	0.65
BenzaClin topical gel	Opaque off-white	17.0	0.77
BENGAY pain relieving gel	Opaque gray-white	7.4	1.6
Finacea gel	Opaque white	0.04	3.5

3.5. Dilution with water

Since emulsions can be diluted with their external phase (Lieberman et al., 1988), 43 creams, lotions and gels were tested to determine if water compatibility could be linked to dosage form. Most products examined had incomplete solubility in water, with particles or clumps of material remaining. Some of the clear gels did dissolve into clear solutions. No trend was observed between solubility and dosage form. The presence of the active ingredient, which is often water insoluble, most likely affected the results of this test.

3.6. High humidity exposure

Exposure to humidity was used as a test of swelling for gels. Gels can swell by absorbing liquid (Marriott, 2001). Creams and gels were tested. Some products gained weight (i.e., clobetasol propionate gels and creams) in the humid environment and some lost weight (i.e., clobetasol propionate emollient creams, Metrogel, BENGAY Pain Relieving Gel and Coppertone Sunblock Gel). No trends were observed between dosage form and gain or loss of weight in a high humidity environment.

4. Discussion

Several of the methods, namely rheology, loss on drying (LOD, a measure of water and volatiles), thermogravimetric analysis (TGA), appearance and composition, distinguished the topical dosage forms in the study. Other methods (specific gravity, surface tension, water absorption, dilution properties, microscopic evaluation and transmittance of visible light) did not adequately separate the dosage forms. Results from the distinguishing methods were used to create a flow chart (Fig. 7) and definition table (Table 3) for determination of dosage form.

Dosage forms are first classified as liquid or semisolid; whereby, solutions, suspensions, and lotions fall under the liquid category and creams, gels, pastes and ointments belong to the semisolid category. Appearance and rheology are used to define the line between liquids and semisolids: liquids flow with little or no external force needed and display Newtonian or pseudoplastic flow behavior; while semisolids do not flow nor conform to the shape of containers and exhibit plastic flow behavior (Marriott, 2001). The flow behavior plots obtained from the Brookfield and Thermo/Haake equipment (Figs. 1 and 2) show similar curve shapes and both figures indicate that much larger shear stresses are necessary to begin the flow for semisolids. The Coppertone Sunblock Gel exhibited liquid behavior and would thus need to be labeled as a solution rather than a gel.

Certain topical products currently marketed as lotions should be relabeled as solutions or suspensions. Solutions are clear, homogeneous liquids, while suspensions are two-phase (i.e., solid-in-liquid) liquids. Using the term solution or suspension rather than lotion would give a practitioner information about the base of a topical drug. The term lotion can then be reserved for those formulations that are liquid emulsions. All three of these liquid dosage forms usually contain aqueous or alcoholic vehicles.

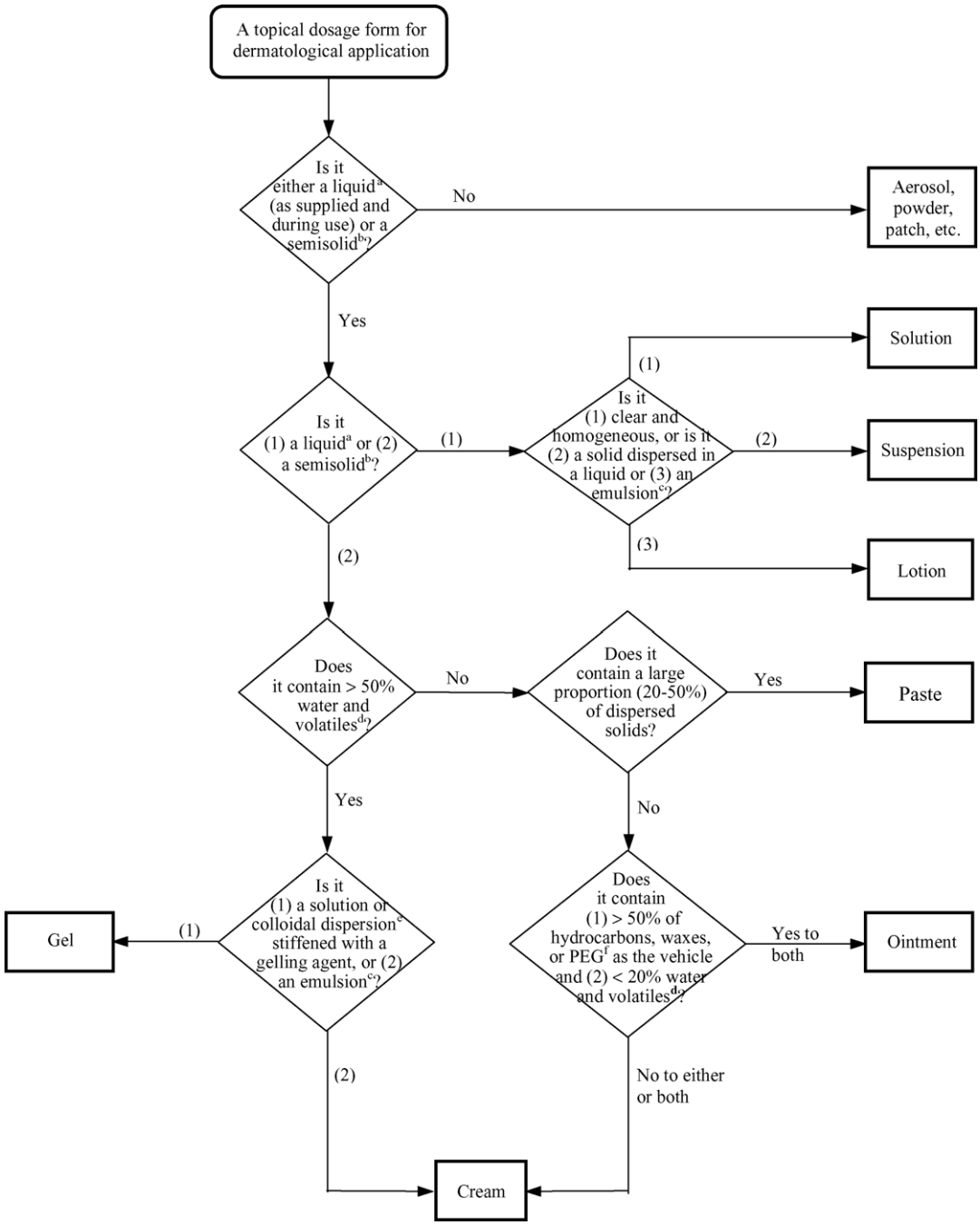

Fig. 7. Decision tree on topical dosage form nomenclature. (a) A liquid is pourable; it flows and conforms to its container at room temperature. A liquid displays Newtonian or pseudoplastic flow behavior. (b) A semisolid is not pourable; it does not flow or conform to its container at room temperature. It does not flow at low shear stress and generally exhibits plastic flow behavior. (c) An emulsion is a two-phase system consisting of at least two immiscible liquids, one of which is dispersed as globules (internal or dispersed phase) within the other liquid phase (external or continuous phase), generally stabilized by an emulsifying agent. (d) Water and volatiles as measured by loss on drying (LOD) test by heating at 105 °C until constant weight is achieved. (e) A colloidal dispersion is a system in which particles of colloidal dimension (i.e., between 1 nm and 1 μm) are distributed uniformly throughout a liquid. (f) Polyethylene glycol.

Table 3
Suggested definitions of topical dosage forms

Dosage form[a]	Definition	Formulation	Appearance and feel	Physical properties
Topical solution	A clear, homogeneous liquid[b] dosage form for external application to the skin	Usually contains an aqueous or alcoholic vehicle; though an oil may also serve as the vehicle. May contain a gelling agent to thicken the solution	Clear, thin	
Topical suspension	A liquid[b] dosage form, that consists of a solid suspended in a liquid vehicle in a two-phase system for external application to the skin	Usually contains an aqueous or alcoholic vehicle	Solid often settles with time, thus requiring shaking before use	
Lotion	An emulsion[c] liquid[b] dosage form for external application to the skin	Usually contains an aqueous vehicle and >50% water and volatiles[d]	Opaque, thin, non-greasy; tends to evaporate rapidly with a cooling sensation when rubbed onto the skin	Exhibits Newtonian or pseudoplastic flow behavior
Gel	A semisolid[e] dosage form that contains a gelling agent to provide stiffness to a solution or colloidal dispersion[f] for external application to the skin. A gel may contain suspended particles	Usually contains an aqueous or alcoholic vehicle and a gelling agent such as starch, cellulose derivatives, carbomers, magnesium–aluminum silicates, xanthan gum, colloidal silica, aluminum or zinc soaps[g]	Usually clear or translucent in a single-phase system; otherwise opaque in a two-phase system; thick, non-greasy; provides a cooling sensation when applied to the skin	Usually exhibits a single transition in TGA[h] corresponding to loss of the vehicle; does not flow at low shear stress and generally displays plastic flow behavior
Cream	An emulsion[c] semisolid[e] dosage form that contains >20% water and volatiles[d] and/or <50% of hydrocarbons, waxes, or polyethylene glycols as the vehicle for external application to the skin	Contains >20% water and volatiles[d] and/or <50% of hydrocarbons, waxes, or polyethylene glycols as the vehicle. There are two types of creams: an oil-in-water cream with water as the continuous phase and a water-in-oil cream with oil as the continuous phase	Opaque, viscous, non-greasy to mildly greasy; tends to mostly evaporate or be absorbed when rubbed onto the skin	Exhibits two or more transitions in TGA[h] indicative of at least a two-phase system; displays plastic flow behavior
Ointment	A suspension or emulsion semisolid[e] dosage form that contains <20% water and volatiles[d] and >50% of hydrocarbons, waxes, or polyethylene glycols as the vehicle for external application to the skin	Contains <20% water and volatiles[d] and >50% of hydrocarbons, waxes, or polyethylene glycols as the vehicle	Opaque or translucent, viscous, greasy; tends not to evaporate or be absorbed when rubbed onto the skin	
Paste	A semisolid[e] dosage form that contains a large proportion (i.e., 20–50%) of solids finely dispersed in a fatty vehicle for external application to the skin	Contains a large proportion (20–50%) of dispersed solids in a fatty vehicle	Opaque, viscous, greasy to mildly greasy; adheres well to the skin, forming a protective layer	

[a] A dosage form is a pharmaceutical formulation that contains a drug substance, i.e., an active pharmaceutical ingredient, and one or more excipients.
[b] A liquid is pourable; it flows and conforms to its container at room temperature. A liquid displays Newtonian or pseudoplastic flow behavior.
[c] An emulsion is a two-phase system consisting of at least two immiscible liquids, one of which is dispersed as globules (internal or dispersed phase) within the other liquid phase (external or continuous phase), generally stabilized by an emulsifying agent.
[d] Water and volatiles as measured by loss on drying (LOD) test by heating at 105 °C until constant weight is achieved.
[e] A semisolid is not pourable; it does not flow or conform to its container at room temperature. It does not flow at low shear stress and generally exhibits plastic flow behavior.
[f] A colloidal dispersion is a system in which particles of colloidal dimension, i.e., between 1 nm and 1 μm, are distributed uniformly throughout a liquid.
[g] For gelling agent information, see Gennaro (2000) and Lieberman et al. (1996b), Chapter 10.
[h] Thermogravimetric analysis.

Creams are also emulsions where water is the continuous phase, but creams are semisolids. Ointments, which are also semisolids, can be emulsions or suspensions. Ointments are separated from creams and gels first on the basis of composition, followed by loss on drying of the vehicle. Ointments are expected to remain longer on the surface of the skin after application than creams or lotions, so a low volatility is desired. An analysis of the products in this study found that a water plus volatiles content of less than 20% generally characterized ointments. This low level of water and volatiles is due to a high hydrocarbon and/or polyethylene glycol content (>50%) in the ointments. Gels are also semisolids. They contain a gelling agent to provide stiffness to a solution or colloidal dispersion. Although gels are often considered clear or translucent, many products that are compositionally gels are found to be opaque because of the presence of an excipient or active ingredient which is not fully soluble in the gel vehicle. In other words, gels may contain suspended particles. Gels are also found to contain aqueous or alcoholic vehicles, which manifest themselves in high levels of water plus volatiles (as measured by LOD) and relatively low temperature TGA curves with a single transition corresponding to the loss of the vehicle. The one gel (mineral oil gel) with a low water and volatiles level was more like an ointment in feel and appearance.

Suggested definitions based on the above conclusions from the products tested are presented in Table 3. Definitions for lotion, cream, ointment, gel, solution, suspension and paste[1] are included. The conclusions can be simplified into a decision tree to facilitate the determination of the most appropriate nomenclature for a dosage form (Fig. 7). Knowledge of composition, a few visual (flow) characteristics and physical measurements (rheology, water plus volatiles as measured by loss on drying) can be used in conjunction with this decision tree to distinguish the topical dosage forms. Use of the decision tree and table will classify products so that practitioners and patients will know what to expect when prescribing or using a topical product. Although the number of topical products examined in this study is limited, the products selected are both representative and encompassing of those in the market, including several borderline or extreme cases, and the results clearly suggest a trend or distinction between dosage forms based on composition and certain physical properties. The future will bring new excipients and new formulation techniques which may require additional knowledge or alternative nomenclature.

[1] The definition of paste was based on a review of properties of currently approved products and literature definitions such as Barry, 2001.

5. Conclusion

Physicochemical properties, especially composition and rheology, can be used to provide a more scientific basis for the classification and distinction of topical dosage forms. Table 3 lists the suggested definitions with physical properties and typical formulations. For firms developing a new topical dosage form, the decision tree in Fig. 7 is designed to assist in determining the correct nomenclature based on physical properties and formulation ingredients. The information generated by these studies and detailed in the table were presented to and endorsed by the FDA Advisory Committee for Pharmaceutical Science in 2003 (see minutes from public meetings held on March 12 and October 22 2003 on the FDA internet). This information is also being considered for inclusion in formal FDA definitions for these topical dosage forms. These definitions may also be applicable beyond dermatological applications (e.g. ophthalmic, otic, vaginal, rectal).

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