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Applied Clay Science 36 (2007) 37 – 50

Applied Clay Science

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Uses of clay minerals in semisolid health care and therapeutic products

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Received 23 March 2006
Available online 13 October 2006

Abstract

Clay minerals are included in several health care formulations. In particular, they are presented in many semisolid preparations with different functions, including stabilization of suspensions and emulsions, viscosizing and other special rheological tasks, protection against environmental agents, adhesion to the skin, adsorption of greases, control of heat release, etc. These functions are possible because of the special disposition of clay mineral particles when dispersed in polar solvents, due to their high surface areas and colloidal dimensions. When necessary, clays are processed or even modified to exalt or change some properties and new clay-like materials with special features are also synthesized. Finally, clays are frequently used concomitantly with other rheological modifiers to obtain synergic effects, influencing the stability and/or other technical properties of the health care products. This paper reviews the properties of clay mineral dispersions and the different functions derived from those properties, providing examples of applications in products intended to fulfil health care aims.

Keywords: Health care products; Pharmaceuticals; Cosmetics; Clay minerals; Semisolids; Gels

1. Introduction

Health is defined as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO Constitution, 1946). According to this definition, health care products should include not only those aimed at treatment of a disease (medicinal products), but also those intended to clean, perfume, change appearance, correct body odors, protect external parts of the body or keep them in good condition (cosmetic products), and even those special foods designed to be consumed as part of the normal diet, but that contain biologically active components offering the potential of enhanced health or reduced risk of disease (functional foods).

Cosmetic products and several medicinal products are designed to be placed in contact with external parts of the human body (epidermis, hair system, nails, lips, etc.) or with the teeth and the mucous membranes of the oral cavity. In these cases they require a consistency suitable for application, and enough viscosity to remain in contact with the application area at least until their objective is achieved. Fluids readily streak and run off

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0169-1317/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.clay.2006.07.006

the desired area and powders have poor staying properties (Patel et al., 1986). However, ideal topical health care preparations must be easily deformed (as a liquid) and retain their shape in repose (as a solid). In order to accomplish this particular behaviour, they must have a three-dimensional structure that is easily broken down, rearranged, and reformed. Consequently, such systems are frequently formulated as semisolids, regardless of their final use or composition.

Semisolid health care preparations include ointments and pastes, creams, gels and rigid foams (Flynn, 2002). Pastes are dispersions of high amounts of solid particles in an ointment (hydrocarbon-based semisolids), creams are oil/water (o/w) emulsions, gels (or jellies) dispersions of a liquid in an interlocking matrix and rigid foams are dispersions of a gas in a liquid phase (Nairn, 1992). These preparations correspond to disperse systems of more than one phase.

Dispersions are heterogeneous systems in which one phase (dispersed, discontinuous or internal phase) is dispersed in a second phase (vehicle, external phase or dispersion medium) (Russel et al., 1995), and both phases may be solid, liquid or gas. These systems have a wide variety of applications in health care products (Tabibi and Rhodes, 1996) including topical semisolids. Dispersions of larger dispersed phases (10–50 μm in size), namely “coarse dispersions”, include most health care semisolid preparations (Nash, 1988; Swarbrick, 1995). Finally, when the size of the internal phase ranges from 1 nm to 1 μm, the system is said to be a “colloidal dispersion”, showing special properties (Everett, 1994). Colloidal particles are of particular interest in some semisolid health care products (Burgess, 1992; Falkiewicz, 1998).

Solid-in-liquid (coarse suspensions and colloidal dispersions) and liquid-in-liquid (emulsions) disperse systems are thermodynamically unstable and the phases tend to separate with time, requiring accurate rheological and stability control. Clay minerals are frequently used in semisolid health care formulations for such purposes, but they are also included with other specific functions, or play more than one role in a formulation. Finally, some semisolid clay formulations include other substances (clays, polymers, etc.) thought to complement the activity of the phyllosilicate.

The amount of clay mineral in a formulation can vary from a small proportion to almost the total final mass. The types of clay used are varied within the selected group of clay minerals used in pharmacy and cosmetics, and strictly controlled by the industries using them and the corresponding administrations (López-Galindo et al., 2006).

The clays used are often natural products merely subjected to treatments ensuring maximum purity and ease of use (desiccation, pulverisation, sieving and wet separation of the clay fraction, sterilization by heat, etc.). In other cases clays are subjected to some chemical process in order to increase a specific property (homoionic clays) or even change their behaviour (organoclays). Finally, there are synthetic materials created from non-clayey substances and imitate clays (Table 1).

The particular use of a clay mineral for any specific application depends firstly on its structure. As a result of their structural and chemical characteristics, both kaolinite and talc show minimal layer charges, presenting low cation-exchange capacities (<15–20 mEq/100 g). On the other hand, smectites are characterized by octahedral and tetrahedral substitutions and high ion-exchange capacities (70–120 mEq/100 g) (Bergaya et al., 2006).

This paper reviews the properties and functions of clay minerals in pharmaceutical and cosmetic preparations of semisolid consistency, providing examples of application in products intended to fulfil different therapeutic or cosmetic aims.

2. Properties of clay mineral dispersions

The main difference in the behaviour of 1:1 and 2:1 clay minerals is their performance when dispersed in polar solvents. 1:1 clay minerals do not swell, in contrast to smectites and vermiculites which create highly structured systems (gels) with interesting rheological properties. Substantial differences arise between 2:1 clay mineral dispersions, depending on particle texture (shape and size), and chemical particularities, as will be discussed below.

2.1. Gel concept and types

Gels are defined as semisolids, being either suspensions of small (colloidal) inorganic particles or large organic molecules (polymers) interpenetrated with liquids (EP, 2005a; USP, 2006a).

Gels are divided into inorganic and organic on the basis of the nature of the colloidal phase. In the first case, the inorganic particles, such as those of 2:1 clay minerals, form three-dimensional structures (“house of cards” or band-type structures) throughout the gel (Abend and Lagaly, 2000). Likewise, the nature of the dispersion medium determines whether a gel is a hydrogel (i.e., water-based), or an organogel (with a non-aqueous solvent). Finally, gels with high concentration of disperse phase are known as xerogels, in which the dispersion medium has been evaporated to leave the

Table 1
Clay minerals used in semisolids health care preparations

Minerals		Pharmaceutical name	Definitions*	Commercial products for health care
Natural clays	Smectites (montmorillonite and saponite mainly)	Magnesium aluminum silicate (USA) or Aluminium magnesium silicate AMS (Europa)	Blend of colloidal montmorillonite and saponite	Gelwhite® MAS grades, Veegum® grades, Carrisorb®, Gelsorb®, Pharmasorb regular®, Bentopharm®, etc.
	Montmorillonite	Bentonite	Colloidal hydrated aluminum silicate/ clay with a high proportion of montmorillonite	Gelwhite® L-NF, Gelwhite®N-NF, Bentolite® MB-NF, Mineral colloid® BP, Mineral Colloid® MO
		Purified bentonite	Colloidal montmorillonite	Veegum® HS
	Hectorite	Used in cosmetics	Hectorite clay	Hectabrite grades, Bentone EW, Bentone MA
	Talc	Talc	Hydrated magnesium silicate	Several
	Kaolinite	Kaolin (USA) or kaolin heavy (Europe)	Hydrated aluminum silicate	Several
	Palygorskite	Activated attapulgite	Heat-treated magnesium aluminum silicate	Attaclay®, Attagel®, etc.
		Colloidal activated attapulgite	Purified magnesium aluminum silicate	Pharmasorb colloidal®
	Sepiolite	Magnesium trisilicate	MgO ($\geq$20%) and SiO_2 ($\geq$45%) with varying proportion of water/$Mg_2Si_3O_8xH_2O$ with MgO ($\geq$29%) and SiO_2 ($\geq$65%).	Alenic Alka®, Recip®, etc.
Modified clays	Modified bentonites	Steralkonium Bentonite	Modified lipophilic phyllosilicates	Claytone® grades
		Quaternary-18 bentonite		Bentone 34, Claytone 34, 40, Claytone XL.
		Quaternary 90 bentonite		
		Quaternium-18 benzalkonium bentonite		Claytone APA, Claytone AF, Baragel 24.
	Modified hectorites	Steralkonium Hectorite		Bentone 27
		Quaternary-18 hectorite		Bentone 38
		Disteardimonium hectorite		Bentone gel® grades
		Dihydrogenated tallow benzylmonium hectorite		Bentone SD-3
		Tromethamite smectite		Veegum® PRO
Synthetic clays		Synthetic hectorite	Sodium magnesium silicate	Laponite® grades

*Definitions taken from EP 5.0, 2005b–f; USP29 and NF24, 2006c–k; and CTFA dictionary, 11th, 2006.

framework behind (Hunter, 1994). Bentonite magma is an example of pharmaceutical inorganic hydrogels (USP, 2006b). This is a true two-phase system, as the inorganic particles of bentonite (nonproprietary commercial name given to those clay materials with a high proportion of montmorillonite) are not soluble in the dispersion medium. It is the interaction between the units of the colloidal dispersed phase (clay particles) which sets up the "structural viscosity" immobilizing the continuous liquid phase.

2.2. Clay-gel formation mechanisms

Gel formation depends on the establishment of a network in which colloidal clay particles are connected in an asymmetric fashion. This requires mutual attraction of the particles (coagulation) and partial wetting by the liquid. In particular, when 2:1 laminar phyllosilicates are dispersed in a polar medium, face–edge and face–face interactions are the two major mechanisms implied in the formation of a rigid network (Van Olphen, 1963; Permien and Lagaly, 1994a,b,c,d; Permien and Lagaly, 1995). On the other hand, modified organoclay gelling mechanisms involve edge-to-edge interactions (NL Chemicals, 1988). The fatty acid chains attached to the face of clay platelets allow the dispersion in the organic medium, while edge-to-edge hydrogen bonding of the platelets (via water bridges) and the interaction of the alkyl chains provide formation of a structure. Finally, fibrous clays (palygorskite and sepiolite) dispersed in water form a three-dimensional structure (gel) composed of interconnecting fibers (Simonton et al., 1988).

2.3. Clay-gel conditions and stability

Addition of water to bentonite does not give any gel. In order to jellify the clay must be sprinkled on the surface of hot water and the dispersion allowed to stand for 24 h, stirring occasionally when the clay has become thoroughly wetted. Bentonite may also be dispersed in water if it is first triturated with glycerin or mixed with a powder such as zinc oxide. High-speed mixing equipment produces satisfactory dispersion of the clay in cold water, but swelling is required in any case to obtain a high viscosity system (Viseras et al., 1999). Smectite gels can swell, absorbing liquids with an increase in volume. It is known that bentonite swells to about 12 times its original volume in water forming a gel, but this does not happen in the presence of organic solvents. Some clay-gels undergo contraction upon standing, expelling the interstitial liquid which collects at the surface of the gel (syneresis).

Smectite gels are sensitive to the addition of electrolytes. Clay mineral particles are negatively charged and flocculation occurs when electrolytes or positively charged suspensions are added. Bentonite is thus said to be incompatible with strong electrolytes, although this effect is sometimes used beneficially to clarify turbid liquids. The effect of ion type and ionic strength on the sol–gel transition of sodium montmorillonite dispersions was studied by Abend and Lagaly (2000). Phase diagrams of different states (sol, repulsive gel, attractive gel, sediment) of the dispersions were obtained, showing that the borderline between gel and sediment depends on the type of counter-ion and co-ion. Ma and Pierre (1999) considered the influence of Fe^{3+} ions on the colloidal behavior of montmorillonite suspensions, concluding that both Fe^{3+} and its hydrolytic products acted as counter-ions to neutralize the electric double layer around clay particles. Fibrous clay-gels retain their stability in the presence of high concentrations of electrolytes, thus making them ideal for such an application (Parkhomenko et al., 1987; Fadat et al., 1988; Eriksson et al., 1990).

2.4. Rheological properties of clay-gels

Clay-gels exhibit characteristics intermediate between liquids and solids and have interesting rheological behaviour (Fig. 1A), including dilatant or more

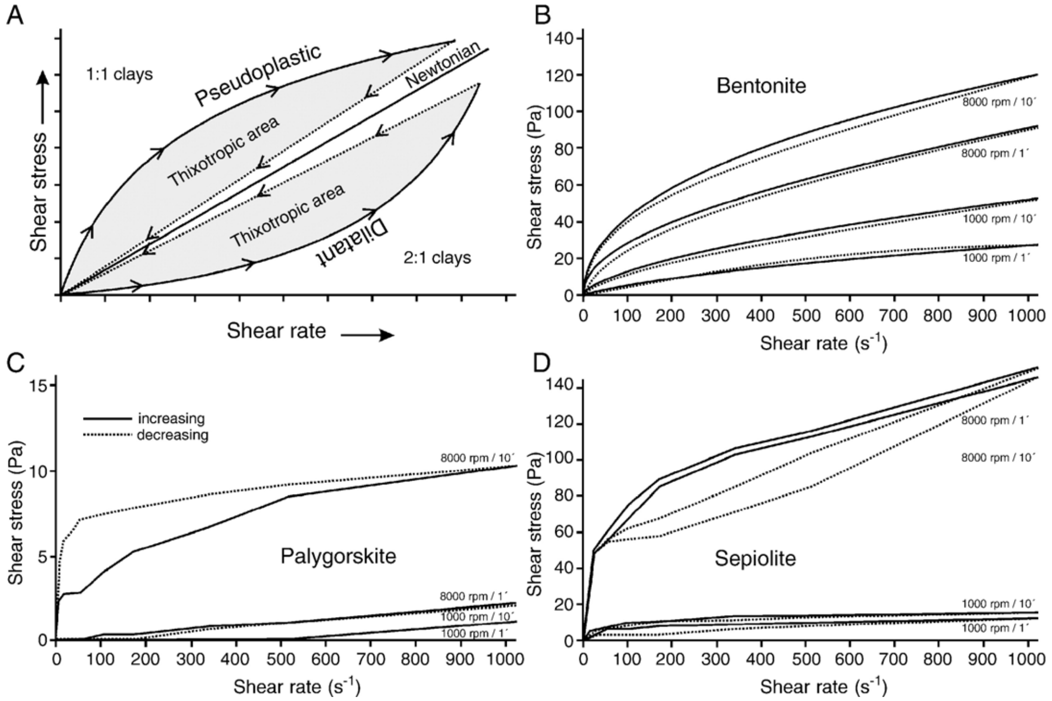

Fig. 1. Flow profiles of clay minerals/water dispersions. A) Ideal profiles of 1:1 and 2:1 phyllosilicate dispersions (modified from Im-Emsap et al., 2002), B, C and D) flow profiles of bentonite, palygorskite and sepiolite water dispersions (10% w/v) prepared under different agitation conditions (1000 and 8000 rpm during 1 or 10 min) (taken from Viseras et al., 1999).

frequently pseudoplastic flows, yield point, thixotropy and high viscosities (Mewis and Macosko, 1994).

At high solid concentrations, kaolin dispersions show dilatant flow (apparent viscosity increases with increased shear rate), with values of viscosity (resistance to flow, expressed as the ratio between shear stress and shear rate) around 300 mPa s, for a 70% w/v kaolin/water dispersion. This rheological behaviour is attributed to close packing of deflocculated clay particles, which during shearing results in interparticle contact and interaction. Lagaly (1989) pointed out the importance of particle morphology and surface charge in the rheological behaviour of kaolin suspensions. Yuan and Murray (1997) compared the rheological characteristics of kaolin dispersions prepared with different crystal morphologies (planar kaolinite and tubular or spherical halloysite), concluding that particle morphologies strongly affected the dispersion viscosities.

On the other hand, dispersions of flocculated solids, as is the case of 2:1 clay minerals, are typically pseudoplastic. Such behaviour is due to progressive breakdown of the system structure. The tenuous structure of inorganic clay particles dispersed in water is disrupted by an applied shear stress. As shear stress increases, more and more interparticle associations are broken, shown as a greater tendency to flow. The colloidal structure of aqueous 2:1 clay mineral dispersions provides their most useful properties: yield point and thixotropy (Lukham and Rossi, 1999). After the clay mineral is hydrated, the three-dimensional network builds rapidly at first, giving a marked increase in viscosity. As time passes, the remaining free platelets take longer to find an available site in the structure, so viscosity increases at a progressively slower rate. Conversely, when a given shear is applied, most of the structure is rapidly disrupted, with subsequent breakdown becoming more gradual. Smectite dispersions are therefore thixotropic: undisturbed they increase in viscosity over time, and under a constant shear rate they decrease in viscosity over time. Smectite dispersions are also pseudoplastic, because increasing the rate of applied shear (thereby increasing structure breakdown) results in decreasing viscosities. The yield point (resistance of the structure to breakdown), assumes that the solid disperse phase remains stable because it would need to exert a certain force (yield value) to move through the dispersion medium. Consequently, the greater the yield value, the more stable the suspension. On the other hand, thixotropy is an important feature for health care suspensions, since apparent viscosity decreases with increase in shear rate and increases again on standing, requiring a certain time for the structure to rebuild.

The viscosity of 5.5% weight/volume (w/v) aqueous bentonite dispersions at 25 °C ranges from 75 to 225 mPa s, increasing with increasing concentration, as also happens with other 2:1 clay minerals (Fig. 2). Other factors greatly influence the final viscosity, including preparation procedure, temperature and presence of other components in the formulation. At $\mathrm{pH} < 6$ viscosity falls when the clay minerals are coagulated by acids. On the other hand, addition of alkaline materials, such as magnesium oxide, increases gel formation and stability. Addition of significant amounts of alcohol will coagulate the clay mineral particles, primarily by compressing the diffuse ionic layer (Lagaly, 2006). Nevertheless, bentonite may be used with concentrations of up to 30% ethanol or 2-propanol, 50% glycerol, 30% propylene glycol, or high molecular weight polyethylene glycols.

Water dispersions of Magnesium Aluminum Silicate (MAS, a commercial product, Table 1) (1–2% w/v) are thin, but increase in viscosity with an increasing concentration of clay. These dispersions exhibit pseudoplastic rheological behaviour with yield value and give the system thixotropic characteristics.

Few investigations have focused on the effects of hydrodynamic factors, such as size and shape of the particles, on the final product properties. Viseras et al. (1999) assessed the effects of shear history on the rheology of laminar and fibrous clay mineral dispersions, concluding that the degree of dispersion and the structural changes resulting from differences in particle shape significantly affect the rheological properties of the systems. A linear relation was found between mixing energy and apparent viscosity of the laminar clay minerals, while apparent viscosity was related to mixing power for the fibrous ones (Fig. 1, B, C and D). A subsequent study examined the filtration behaviour of some Spanish clay–water dispersions, the results of

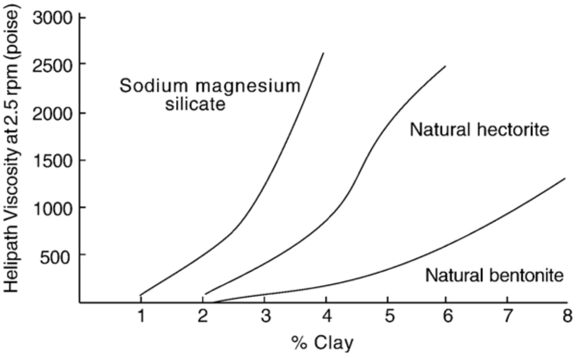

Fig. 2. Influence of clay concentration on viscosity profiles of bentonite and natural or synthetic hectorite (modified from Clarke, 1993).

which were compatible with the rheological properties of the systems (Viseras et al., 2001).

3. Functions of clay minerals in semisolid systems

As pointed out before, clay minerals have two major functions in semisolid formulations— they stabilize solid-in-liquid or liquid-in-liquid disperse systems, and adjust the rheology patterns of the preparations. These tasks are intimately linked to the presence of charges on the surface of the clay mineral particles, their colloidal dimensions, and their ability to form “special structures” when dispersed in polar media.

Nevertheless, stabilization of dispersions, suspensions or emulsions appears not only as a result of the gel-forming abilities of clay minerals, but also because of their presence on interface boundaries due to their colloidal size, surface charges, and high surface areas (Clarke, 1994). On the other hand, the rheological properties of clay dispersions are strongly dependent on the type of clay mineral, concentration, and presence of other molecules and ions and not necessary linked to stabilization of the formulation.

The functional properties of clays (high thixotropy, shear thinning, thermally reversible, suspension, viscosity, emulsion stability and syneresis control) lead to their use in several semisolid products, including lotions, creams, ointments, pastes and make-up preparations, etc. (Table 2).

3.1. Suspension additives: wetting agents

3.1.1. Objective

The addition of solid particles to the dispersion medium is the critical step in preparation of health care suspensions, and requires adequate wetting of the solid particles (Fig. 3). Most drugs are hydrophobic and, when suspended, frequently float on the vehicle surface due to poor wetting. Bentonite and MAS are reported to aid dispersion of hydrophobic drugs.

3.1.2. Examples of use

Kaolin is blended with sulfur and then dispersed in the heated oil phase. The oil phase is then emulsified with an aqueous phase to obtain a sulfur ointment. (Sarfaraz, 2004a). Both MAS and bentonite are also included as wetting agents in pigmented foundation creams. The main difficulty in preparing these creams is the homogenous dispersion of the pigments to give reproducible colors. Depending on the relative amount

Table 2
Functions and applications of clays in semisolids health care products

Pharmaceutical name	Functions	Applications
Magnesium aluminum silicate (USA) or aluminium magnesium silicate (Europe)	Rheological additive	Ointments
	Gelling agent, stability	Topical, Pigment suspensions
	Rheological additive	Toothpastes
	Emulsion stability additive	Lotions
	Suspension additive	Pastes
Bentonite and purified bentonite	Thickener and suspending	Topical suspensions
	Emulsion stability additive	Lotions
	Thickener, suspending, thixotropy	Liquid Make-up
Hectorite	Thickener, suspending, thixotropy	Lotions, shampoos, liquid make-up
Talc	Filler, adsorbent, protection agent, etc.	Creams, pastes, etc.
Kaolin (USA) or kaolin heavy (Europe)		
Activated attapulgite	Thickener, suspending, thixotropy, emulsifying	Topical suspensions, pastes, creams, etc.
Colloidal activated attapulgite		
Magnesium trisilicate		
Steralkonium bentonite	Gelling in non-polar organic solvents	Anti-perspirants, lotions,
Quaternary-18 bentonite		suntan products, nail lacquers, lip products
Quaternary-18 benzalkonium bentonite		
Steralkonium hectorite		
Quaternium-18 hectorite		
Disteardimonium hectorite		
Dihydrogenated tallow benzylmonium hectorite		
Tromethamite smectite		
Synthetic hectorite	Viscosity, thixotropy, short texture	Toothpaste
	Thixotropy	Lotions
	Viscosity, thixotropy	Shampoos
	Suspension	Liquid make-up

*Functions and applications taken from EP 5.0, 2005b–f; USP29 and NF24, 2006c–i; or supplier descriptions.

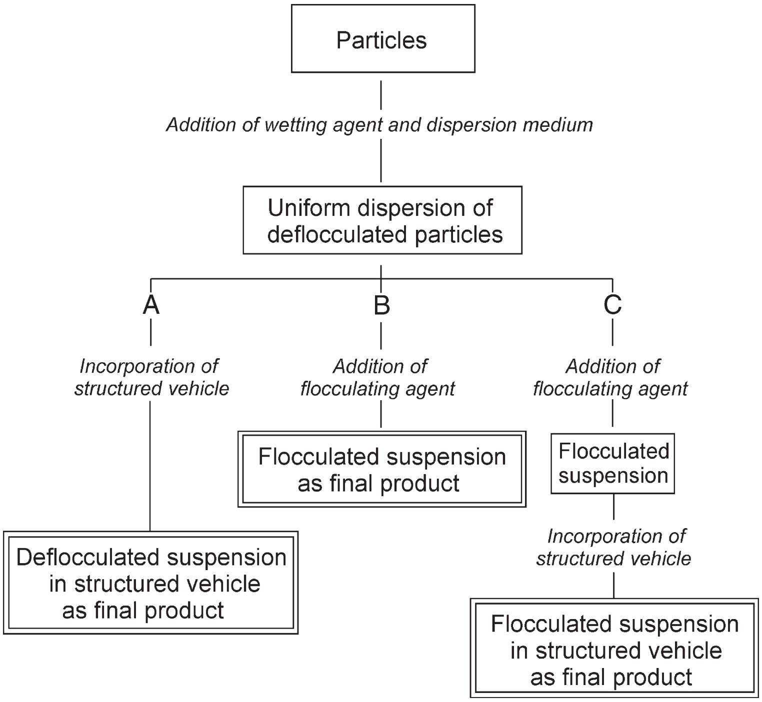

Fig. 3. Alternative approaches to the formulation of suspensions (taken from Swarbrick, 1995).

of the pigments, the cream may be used as a suitable adherent base (foundation) for the powder used as make-up (3–10% of pigments) or directly as a complete make-up (10–25% of pigments) (Gabriel, 1973).

3.2. Suspension additives: suspension stability agents

3.2.1. Objective

The stability of these preparations may be defined as the ability of the formulation in a specific container to remain within its physical, chemical, microbiological, therapeutic or cosmetic, and toxicological specifications. Suspending and anti-caking agents are used to prevent drastic changes in dispersion properties, retarding sedimentation or producing flocculation of the suspended particles that, although they settle rapidly, are easily resuspended by low agitation. They may be used alone, or in combination. Their selection is based on suspending/anti-caking ability, compatibility with the rest of formulation, pH tolerance, appearance, source, reproducibility and cost.

3.2.2. Mechanism

Suspending agents are used to retard sedimentation by affecting the rheological behaviour of a suspension (Fig. 3). An ideal suspending agent should produce a structured vehicle, have high viscosity at low shear rates, not be affected by temperature or ageing, be able to tolerate electrolytes, be applicable over a wide pH range, exhibit yield stress, be compatible with other components in the formulation and be non-toxic.

When particles are held together strongly they are called aggregates. Isolated particles and aggregates settling on the bottom of a container become compacted, forming a cake, which is a major problem in suspensions containing a high concentration of solids. Caking cannot be eliminated by reducing the particle size or increasing the viscosity of the medium, but it can be anticipated and prevented. When the particles are held together in a loose, open structure, the system is said to be in a state of flocculation. Flocculated particles settle rapidly to form a large of volume sediment, but are readily redispersed.

Electrostatic stabilization due to repulsion between the diffuse ionic layers around the charged particles is a well-known effect. A dispersion is stable when the potential energy of repulsion arising from the approach of charged particles exceeds the inherent attractive energy between the particles over a given distance of separation (Mathews and Rhodes, 1970; Russel et al., 1995; Lagaly, 2006).

3.2.3. Examples of use

The use of kaolin and talc as suspending and anti-caking agents has been reviewed by Kibbe (2000). A kaolin–pectin suspension also including MAS (type IA) is used as suspending agent. MAS is first dispersed in water and then kaolin is added under constant mixing at 70 °C until evenly dispersed. Finally pectin is added and viscosity adjusted with carboxy methylcellulose (CMC). The final product must be allowed to cool and stand overnight to hydrate (Sarfaraz, 2004b).

Bentonite is used as suspending agent at concentrations ranging from 0.5 to 5% w/v. At 1.7% w/v, the clay produced very good flocculation of bismuth subnitrate suspensions (Schott, 1976). Both bentonite and purified bentonite (colloidal fraction processed to remove grit and non-swellable ore compounds) are used as suspending agents, resulting in suspensions with approximately 9.5–10 pH (2% w/v). The gelling properties of bentonites are reduced by acids, but increased by alkalies such as magnesium oxide. Vanderbilt Ltd. commercializes a bentonite under the name Veegum HS, proposing several health care formulations including this clay (Vanderbilt Report, 1984). Purified bentonite (Veegum HS) is included as suspending agent in antacid suspensions (5 mg/mL), in combination with xanthan gum to obtain the adequate viscosity (Sarfaraz, 2004c).

MAS is a good suspending agent as it prevents sedimentation without affecting pour-ability or spreadability of the suspension. Four types of MAS (IA, IB, IC, IIA), with different viscosity and Al/Mg ratio contents, are commercialized and recognized by the pharmacopoeias (USP, 2006c). MAS (Magnabrite S) is reported as suspending agent at 10 mg/mL concentration (Sarfaraz, 2004d). Magnabrite K (15 mg/mL) is included in a bismuth subsalicylate suspension and mixed with an aqueous dispersion of methylcellulose to obtain a smooth gel incorporating the rest of components (Sarfaraz, 2004e). In other cases, MAS (Veegum HV) is used as gelling agent in suspensions (Vanderbilt Report, 1984; Sarfaraz, 2004f).

Palygorskite absorbs polar liquids to form gels, or is dispersed in water to give suspensions with 9.5 pH (5% w/v aqueous suspension). The clay mineral is heated to increase the adsorptive capacity (activated attapulgite) and processed to select particle sizes lower than 2 μm (colloidal activated palygorskite). All three grades of the phyllosilicate are used in semisolid formulations as suspension agents (Sweetman, 2005).

3.3. Suspension additives: suspension viscosity agents

3.3.1. Objective

Clays are also used as rheological modifiers (Fig. 3). Physical stability of a suspension can be improved by increasing the viscosity of the external phase, as the rate of sedimentation (according to Stokes equation) is an inverse function of viscosity. Linked to their particular behaviour when dispersed in polar media, clay minerals are used to adjust rheology in semisolid preparations.

3.3.2. Mechanism

Modification of the final rheology in preparations will depend on the type and amount of clay mineral incorporated. As mentioned above, 1:1 clay mineral dispersions show dilatant behaviour (higher viscosity as shear increases, as in the case of kaolin slurries), whereas 2:1 clay minerals show pseudoplastic behavior (lower viscosity as shear increases, with shear thinning directly proportional to shear rate). Viscosity returns to normal on release of shear stress. Some 2:1 clay mineral dispersions return to initial viscosity immediately, but other systems require some time to do so (thixotropic dispersions).

3.3.3. Examples of use

Some types of laminar and fibrous 2:1 clays are particularly useful as stabilizers (El-Halabi, 1977; Chang et al., 1993; Miano and Rabaioli, 1994; Viseras et al., 1999, 2001), including blends of montmorillonite and saponite commercialized as MAS, almost pure montmorillonite (bentonite) and fibrous phyllosilicates (palygorskite, also known as attapulgite; and sepiolite, commercialized as magnesium trisilicate, López-Galindo et al., 2006). The thickening efficiency of 2:1 clay minerals follows the order MAS > hectorite > bentonite (Clarke, 1994).

MAS dispersions in water at the 1–2% w/v level are thin colloidal dispersions. At 3% w/v and above, the dispersions are opaque. As concentration increases above 3% w/v, the viscosity of aqueous dispersions increases rapidly and the dispersions become thixotropic; 4–5% w/v dispersions are thick, white colloidal sols, and at 10% w/v firm gels are formed. Calamine lotion could be prepared by using MAS as stabilizing (gelling) agent and to suspend the oxide actives (flocculating agent) (Vanderbilt, 2006a). The viscosity of MAS dispersions, stable between pH 6 and 11 increases with heating or addition of electrolytes, and at higher concentrations by ageing. Electrolytes also thicken MAS dispersions because the clay mineral particles are partially coagulated, increasing both viscosity and yield value (Falkiewicz, 1998).

Hectorite is also used as suspension stabilizer (Ash and Ash, 2002), and polyethylene glycols increase the consistence of hectorite dispersions (Omar et al., 1994). Finally, the clay mineral has been modified to obtain quaternary C 18 hectorite, steralkonium hectorite, etc., used as viscosity controlled agents in organic media, and even synthesized from non-clayey materials (Clarke, 1994).

3.3.4. Clay–polymer synergism

Clays are used either alone or, more frequently, in combination with other suspending agents such as cellulose derivates and natural gums. Polymers used in combination with clays to enhance the rheological properties of both the clay and the organic compound include cellulose gums (carboxy methylcellulose, CMC) and hydroxy ethylcellulose (Ciullo and Braun, 1992), xanthan gum (Ciullo, 1981), and carbomers (Braun, 1991). Examples of this synergism include MAS and sodium alginate in a griseofulvin suspension (Grifulvin, 1985) and bentonite and carboxy methylcellulose in a sulfamethoxazol/trimethoprim suspension (Dechow et al., 1976).

MAS is used in topical formulations as a suspending and stabilizing agent either alone or in combination with other agents (Syman, 1961; Polon, 1970; Farley and Lund, 1976; Attama et al., 1997). Addition of CMC provides synergistic viscosity effect (Fig. 4), and good electrolyte tolerance, combining the high yield value of MAS and the smooth flow properties of CMC. As flocculated MAS enhances the stability of disperse systems with CMC and others gums, a blend of MAS and CMC is currently prepared and commercialized as Veegum PLUS (Vanderbilt, 2006b). Xanthan gum provided synergism with MAS in both viscosity and yield value (Kovacs, 1973, Ciullo, 1981). Concomitant use of MAS and this polysaccharide in semisolid formulations dried quickly, remaining in contact with the skin (Vanderbilt, 2006c, d, e).

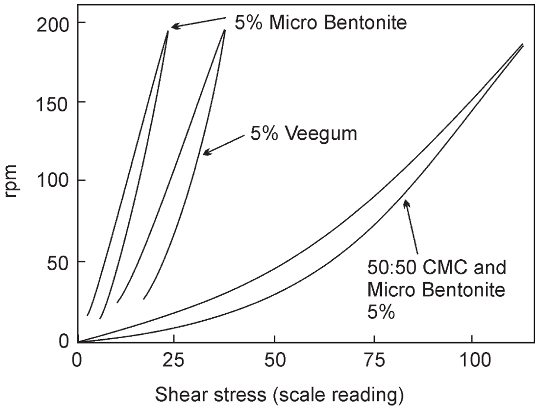

Fig. 4. Flow curves of bentonite, magnesium aluminum silicate and physical mixture of bentonite and Carboxy methylcellulose (modified from Martin, 1993).

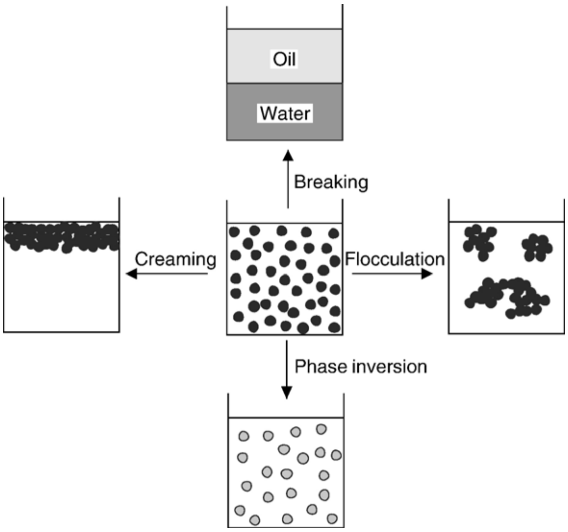

Fig. 5. Schematic illustration of different types of instability of emulsions (modified from Im-Emsap et al., 2002).

3.4. Emulsion additives

3.4.1. Objective

Many health care semisolid formulations are three (or more) phase emulsions. Following emulsification, emulsion stabilization can be achieved through interference with creaming, droplet flocculation, coalescence (breaking), or phase inversion (Fig. 5). These objectives may be attained by equalizing phase densities, increasing the viscosity of the continuous phase, or by adsorbing stabilizing substances at the oil/water interface.

3.4.2. Mechanism

Clays are used as thickening (viscosizing) and emulsifying agents in emulsions due to their ability to be wetted by the two liquid phases, located at the liquid–liquid interface and to act as a physical barrier to prevent coalescence of the liquid droplets (Fig. 6). Because clay particles are electrically charged, the electric double layer further assists in stabilization against flocculation (Friberg et al., 1995).

Regarding mechanical protection against coalescence, the contact angle at the oil–water–solid interface will determine the stabilizing effect: the higher the contact angles, the higher the stabilization of the emulsion (Fig. 6). The energy required to displace a particle from its position at the interface into the droplets is reduced greatly with contact angles less than 90°. Such contact angles between the solid and one of the liquid phases require the addition of small amounts of surface-active agents able to bind strongly to the solid surface,

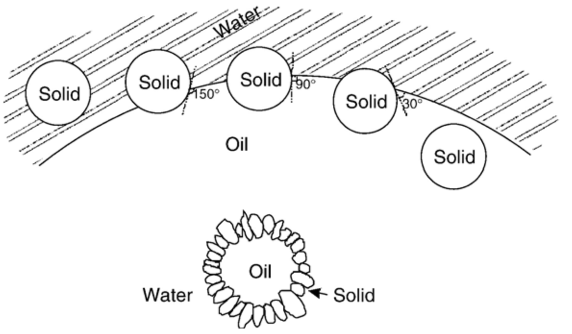

Fig. 6. Schematic illustrations of clay emulsifying mechanisms (taken from Friberg et al., 1995).

but not enough to reduce the interfacial tension at the water–oil interface.

3.4.3. Examples of use

Talc (4% w/v) is used as emulgent in "make-up preparations" because of its ability to locate at the interface between the two liquids, as a result of its high surface area (Gabriel, 1973). Kaolin is used in a complex sulfur antiseptic ointment. It is used as protective agent (in amounts of 85 mg/g), mixed with sulfur and dispersed in the oil phase of the final emulsion (Sarfaraz, 2004g).

Bentonite is used to prepare cream bases containing oil-in-water emulsifying agents. It is included in oil-in-water systems as a protective colloid to stabilize the emulsion, because of its ability to collect at the interface boundary separating the two liquid phases. Carter (1940) proposed a formulation for a nail-enamel remover cream including bentonite as emulsifier at 4% w/v. According to the author, the clay should be mixed with 20% of the water phase and allow to stand for 12 h. The rest of the components are then mixed with the suspension under continuous agitation, and the clay is expected to swell during standing time. Bentonite (2.5% w/v) is also included as emulgent in oil-in-water make-up (Gabriel, 1973) or in vanishing low oil-content creams (Alexander, 1973a). Because of its thixotropic properties it is included in corn and callus emulsions, allowing easy application of the preparation under stress, and permanence in contact with the skin (Alexander, 1973b). Hand creams are used to provide a source of moisture to the skin, leaving the skin soft but not sticky or greasy. They can be thickened by the addition of bentonite (5–10% w/v) and this gives to the continuous phase a little extra rigidity which results in better moisture control (Harry, 1973). Veegum© is used in liquid eyeliner formulations as viscosizant (Alexander, 1973c). Cleansing lotions with benzoyl peroxide have been formulated including Purified Bentonite (Polargel NF©) as emulsifier. The clay must be sifted in water with rapid mixing and allowed to hydrate for 15 min, when the suspension is passed through a coarse sieve and mixed with hydroypropyl methylcellulose until all lumps are removed. The resulting suspension is emulsified with the oil phase of the lotion, resulting in 40 mg/g clay in the final product (Sarfaraz, 2004h). Instead of a lotion, a cream with the same active substance can be prepared by using more viscosizing agents (including carbomer and increasing clay to 140 mg/g) (Sarfaraz, 2004i).

MAS (Veegum© Regular) is included in resorcinol anti-acne cream emulsions (Sarfaraz, 2004k). MAS is dispersed by vigorous agitation in deionized water to obtain a gel. After addition of water soluble components, this phase is heated and emulsified with fused oils to obtain a cream or a lotion depending on the relative amount of water (Sarfaraz, 2004l). MAS is also proposed for use in burn cream emulsion, (Sarfaraz, 2004m, n), analgesic methyl salicilate creams (Sarfaraz, 2004o) as well as in zinc oxide (Sarfaraz, 2004p) or in zirconium oxide lotions (Sarfaraz, 2004q) and in zinc undecylenate creams (Sarfaraz, 2004q), amounts varying from 7 to 15 mg/g.

Palygorskite is also used as emulgent at around 2–5% w/v (Wenninger et al., 2000). Again, the clay is first suspended in water under intense agitation and the resulting smooth gel is used to incorporate the rest of components and emulsify with the oil phase.

3.4.4. Clay–polymer synergism

Regarding combinations with other agents, Ciullo (1981) found a synergic effect of smectites and natural gums as stabilizers in the formulation of emulsions. A similar effect was also found with carbopol (Ciullo and Braun, 1991). Lagaly et al. (1999a,b) studied the use of smectites in combination with non-ionic surfactants as stabilizers in the formulation of oil in water emulsions. As discussed above, the main stabilization mechanism proposed by these authors was the formation of a mechanical barrier around the oil phase droplets, preventing their coalescence.

MAS is included in a vitamin-enriched skin cream with natural moisturizers because of its emulsifying ability (Vanderbilt, 2006f). Xanthan gum is also included in the formulation to collaborate with the silicate, reducing tackiness and improving emulsion stability, maintaining the viscosity of the product. MAS/CMC dry blends in the ratio 15 mg/3 mg are slowly added to water (796, 50 g) to obtain a gel used in a Zirconium Oxide Lotion (Sarfaraz, 2004r).

3.5. Others functions of clay minerals in semisolid formulations

3.5.1. Fillers

Talc is included as diluent in anti-fungal semisolid preparations (Alexander, 1973b) and aluminum silicate and mica are used as fillers up to about 25% w/w of the solid compositions in plastic fingernails (Alexander, 1973d). A bioadhesive gel is prepared by using a bentonite (Polargel©) as filler and Karaya gum as viscosizing agent (Sarfaraz, 2004s). Finally, MAS is included in a toothpaste as filler, acting also as abrasive agent able to clean tooth surfaces (Vanderbilt, 2006h).

3.5.2. Control of heat-release agents

Peloids can be defined as natural medicinal products of semisolid consistency, resulting from the interposition of organic and/or inorganic solids in medicinal mineral water. When suitably prepared and administered topically as local applications or baths, and because of a number of biophysical and/or biochemical actions, they are used therapeutically for the treatment or prevention of certain pathologies or to correct their effects on the organism (Torresani, 1990; Veniale, 1997; Cara et al., 2000a,b; Veniale et al., 2004; Viseras and Cerezo, 2006). The properties of these suspensions that make them therapeutically useful are essentially adsorptive, rheological and thermal.

The first two of these are related to the high specific surface area of the clays, which encourages adhesion to the skin, and the high viscosity and thixotropic properties of the systems, which allows them to be extended over a localised area with which they remain in close contact until removed. Finally, after heating, peloid suspensions cool slowly, releasing heat progressively and over a considerable period (Cara et al., 2000a,b).

Peloids need a period of maturation, normally ranging from 3 to 6–12 months. After maturation they are applied as baths or locally in 1–2 cm thick layers on parts of the patient's epidermis at a temperature of 40–45 °C for 20–30 minute sessions. Treatment lasts from one to several weeks, depending on the therapeutic aim (Veniale, 1997). The effects depend on the temperature, duration and extension of the application. It is accepted that the main mechanism of peloids' effects is thermotherapeutic. Its low rate of heating and cooling in comparison with mineral medicinal water alone allows it to be applied at higher temperature with an increase in length of the thermal effect. Its effects are sedative, relaxing, anti-inflammatory and analgesic in the area treated, due to vasodilation, increased perspiration and stimulation of the cardiovascular and respiratory apparatus (Bellometti et al., 1996, 1997, Bellometti and Galzigna, 1998).

3.5.3. Adsorption and cleaning agents

3.5.3.1. Objective. Face pack and masks are applied to the face in the forms of liquid or pastes, allowed to dry or set with the aim of improving the appearance of the skin. Their effects are both psychological and cleansing. These systems must be smooth, without gritty particles, have a homogeneous color, once applied must dry rapidly, and must have good skin adhesion but also be easily removed by peeling off the face without pain. Obviously, they must be dermatologically innocuous and non-toxic, and ideally, they must clean the skin and produce a sensation of tightening after application. There are four basic types of face packs and masks: wax-based systems, rubber-based systems, hydrocolloid-based systems and clay-based systems.

3.5.3.2. Mechanism. The clays included adsorb grease and dirt from the facial skin. Face masks are usually left on the face for about 10–25 min, to allow most of the water to evaporate and the resulting clay film to contract and harden, after which they are removed (Alexander, 1973e).

3.5.3.3. Examples. Finely ground talc is the main and often the only constituent of baby powders, since it provides slip and helps lubricate the surface of the skin (Wedderburn, 1973). It also adheres well to the skin and does not plug the sweat and sebaceous orifices. The recommended particle size of talc is between 10 and 40 µm, and the variety with rounded platelets is preferred to granular or fibrous varieties. Because talc does not readily absorb moisture, other ingredients are included (kaolin, hydrated aluminum silicate, magnesium carbonate and starches), and kaolin is used in these preparations by its absorption and adhesive properties (Alexander, 1973f). An electrolytically purified grade of kaolin, known as Osmokaolin, is a very fine, soft powder which takes up moisture readily. It does not have the slip properties of talc and is used at concentrations under 30%.

The hands must be thoroughly cleaned in many occupations to avoid the risk of irritation, infection or contact dermatitis due to prolonged contact with contaminants. Cleaning preparations vary depending on the type of contaminant (contact adhesives, oils, solvents, etc.). MAS has been proposed in a waterless hand cleaner cream (Alexander, 1973g, Vanderbilt, 2006g), useful when water is not readily available but oil, grease and stains must be removed (e.g., motorists and lorry drivers).

3.5.4. Protective agents

Clays are widely used in protective creams. Although such creams differ in composition according to the particular class of hazard against which protection is desired (dust, water, grease, sun, etc.), they should be easy to apply and form a continuous, coherent and impermeable, but flexible film, and must protect the skin, ensuring that it is hydrated and the pH is maintained. 1:1 phyllosilicates are included in various barrier preparations to provide protection against water soluble irritants. Kaolin and talc are used in protective creams (Alexander, 1973g), providing a mechanical barrier to dry dust irritants. Sterilized kaolin (20% w/v) and Fuller's earth (2% w/v) are included for protective purposes in a water miscible barrier preparation, recommended by the Barrier Substances Subcommittee of the BP Codex (Sweetman, 2005). Finally, clays are also used in sunscreen products, designed to provide sun protection by either scattering or absorbing radiant energy. Kaolin and talc are used for their scattering properties (Juch et al., 1994).

3.5.5. Adhesion and softness

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc may contain microorganisms and should be sterilized when used as a dusting powder. It adheres readily to the skin and is soft to the touch and free from grittiness. Talc (20% w/v) is used in a sulfide chemical depilatory formulation (Alexander, 1973f) and at higher concentrations (69% w/v) is included in foot powders to give slip (Alexander, 1973c).

4. Concluding remarks

Clays are used in semisolid health care preparations with different purposes, including topical administration of active molecules, cosmetic effects, heat-therapy or protection against environmental agents. This is due to the special properties of their aqueous dispersions, as well as their capacity to accumulate preferentially in the separation interface between the phases of liquid–liquid disperse systems. Likewise, clay minerals appear in semisolid formulations with specific functions related to other properties, such as their capacity to absorb different substances, their slow cooling rate, or their interference of solar radiation.

On the basis of natural clays, which have been in use since antiquity, new materials have been developed that modify their initial hydrophilic character or imitate clays, thus widening the field of use of clays and/or improving their already excellent behaviour and utility.

In some fields there have been remarkable advances in the understanding of the mechanisms determining possible applications of clays in semisolid forms, such as the stabilization of disperse systems. Further research is necessary, however, on their influence on cooling kinetics, interaction of discreet or polymer organic molecules, or interference with solar radiation, with a view to improving their health applications.

Acknowledgements

This paper received support from DGES project MAT2003-06606 and Group RNM-0179 of the Junta de Andalucía (Spain). We wish to express our gratitude to Prof. Ian MacCandless (Department of English and German Philology, University of Granada) for assisting us with the English version of the text.

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