Applied Clay Science 46 (2009) 73–80

Contents lists available at ScienceDirect

Applied Clay Science

journal homepage: www.elsevier.com/locate/clay

Clay and non-clay minerals in the pharmaceutical industry Part I. Excipients and medical applications

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ARTICLE INFO

Article history:
Received 11 March 2009
Received in revised form 17 July 2009
Accepted 22 July 2009
Available online 29 July 2009

Keywords:
Minerals
Pharmaceutical industry
Excipients
Medical applications
Physical and physico-chemical properties

ABSTRACT

Minerals are widely used in the pharmaceutical industry as lubricants, desiccants, disintegrants, diluents, binders, pigments and opacifiers, as well as emulsifying, thickening, isotonic agents, and anticaking agents, and flavour correctors and carriers of active ingredients.

A variety of minerals are used as excipients in pharmaceutical preparations because they have certain desirable physical and physico-chemical properties, such as high adsorption capacity, specific surface area, swelling capacity, and reactivity to acids. Other important properties are water solubility and dispersivity, hygroscopicity, unctuosity, thixotropy, slightly alkaline reaction (pH), plasticity, opacity, and colour. Clearly such minerals must not be toxic to humans. The following minerals are commonly used as excipients: oxides (rutile, zincite, periclase, hematite, maghemite, magnetite), hydroxides (goethite), carbonates (calcite, magnesite), sulfates (gypsum, anhydrite), chlorides (halite, sylvite), phosphates (hydroxyapatite), and phyllosilicates (palygorskite, sepiolite, kaolinite, talc, montmorillonite, saponite and hectorite). More recently, some tectosilicates (zeolites) also feature in pharmaceutical preparations.

Minerals also enjoy the following medical/health applications: a) contrast diagnostic techniques, b) production of dental cements and dental molds in odontology, c) immobilization of limbs and fractures or dental and craniofacial surgical procedures in traumatology, d) bone grafts or construction of orbital implants, and e) spas and aesthetic centers. Examples of such minerals are oxides (zincite, magnetite and maghemite), sulphates (gypsum and barite), phosphates (hydroxyapatite) and phyllosilicates (clay minerals).

1. Introduction

Minerals are used in pharmaceutical preparations as either active ingredients (having therapeutic properties), or excipients. Whereas this paper deals with the use of minerals as excipients, a companion paper (next issue) reviews their use as active ingredients. Excipients are more or less inert minerals that determine the consistency, form, and volume of the pharmaceutical preparations. Some excipients have organoleptic properties (e.g., colour), induce liberation of the active ingredient within the organism, or facilitate the elaboration and conservation of the pharmaceutical preparation. Minerals also enjoy diagnostic, odontological, and traumatological applications, and are used in spas and aesthetic centers for therapeutic proposes (Fig. 1).

Although the market volume for pharmaceutical minerals is small, the added value is substantial, since the price of pharmaceutical grade minerals may be up to ten times that of the same minerals dedicated to other uses. This is because pharmaceutical minerals must meet the strict chemical, physical, and toxicological specifications set out in the European or United States Pharmacopoeia (López Galindo et al., 2007). Purification treatments, such as particle size fractionation, thermal treatment, and acid activation, improve the physical and physico-chemical properties of the minerals in question.

The majority of crystalline substances, used as either active ingredients or excipients, are synthetic analogues of the naturally occurring minerals (Carretero and Pozo; next issue). The few natural minerals that feature in pharmaceutical applications are there because they are abundant and inexpensive (e.g., calcite, halite, gypsum), or because their synthesis is complicated and costly (e.g., clay minerals).

The papers published until now related with minerals used in pharmaceutical industry show that besides being non-toxic to humans, some pharmaceutical minerals should have a high adsorption capacity, specific surface area, and swelling capacity as well as thixotropic and colloidal properties (Galan et al., 1985; Veniale, 1992; Bolger, 1995; Veniale, 1997; Carretero, 2002; Love, 2004; López Galindo and Viseras, 2004; Carretero et al., 2006; Droy-Lefaix and Tateo, 2006; Carretero and Pozo, 2007; Lefort et al., 2007; Viseras et al., 2007). No comprehensive review, however, is available on the all physical and physico-chemical properties of minerals that are used in the pharmaceutical industry.

The use of clay minerals and non-silicate minerals as excipients in pharmaceutical formulations has been described by many authors

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doi:10.1016/j.clay.2009.07.017

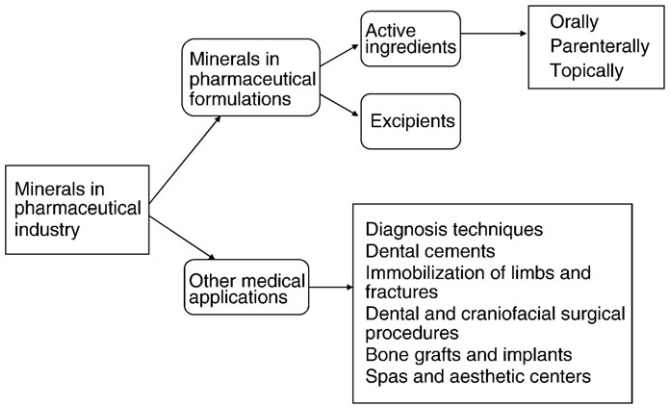

Fig. 1. Minerals in pharmaceutical industry.

(Galan et al., 1985; Veniale, 1992; Bolger, 1995; Veniale, 1997; Carretero, 2002; Cerri et al., 2004; Love, 2004; López Galindo and Viseras, 2004; Carretero et al., 2006; Droy-Lefaix and Tateo, 2006; Carretero and Pozo, 2007; Del Hoyo, 2007; Lefort et al., 2007; Viseras et al., 2007, and references therein). Not all the minerals mentioned in the Pharmacopoeias, however, were included. Here we provide a comprehensive review on the use of minerals as excipients in pharmaceutical preparations, together with those used for diagnostic and other medical purposes. We have reviewed the papers published until now (and the references therein) so as the Pharmacopoeias. In each case, we attempt to correlate the physical and physico-chemical properties, and chemical composition of the minerals with their use in the pharmaceutical industry and/or health care centres.

2. Physico-chemical and physical properties of minerals used in the pharmaceutical industry

The most important physico-chemical properties of minerals used in pharmaceutical industry are surface reactivity (adsorption, cation exchange, swelling), rheology, acid-absorbing capacity, and solubility (HCl, H_2O). Because of their small particle size, large specific surface area, and peculiar charge characteristics, clays and clay minerals have interesting surface properties. Fig. 2a shows the external specific surface areas of representative clay minerals, measured by adsorption of N_2 gas at 78 K, and applying the Brunauer–Emmett–Teller (BET) equation. Fig. 2b gives the total (external and interlayer space) specific surface areas of different clay minerals and metal (hydr)oxides, measured by adsorption of polar organic compounds.

Clay minerals exhibit ion exchange behavior, as do zeolites, colloidal metal (hydr)oxides, and natural organic matter (humic substances). The CEC values for a range of clay minerals are shown in Fig. 3.

The ability of smectites, notably Na^+-montmorillonite, to swell in water in two phases has been well documented (van Olphen, 1977; Madsen and Müller-Vonmoos, 1989).

The rheological properties (e.g., dispersion, swelling, viscosity) of minerals are important to many industrial and pharmaceutical applications, while the mechanical properties (e.g., plasticity) of clays determine their usefulness in health-related applications (e.g. pelotherapy).

The rheology of clay mineral dispersions has been reviewed by Güven and Pollastro (1992). Of special interest are the flow behaviour and stability of clay dispersions, and the time-dependent deformation of clays in a solid or semi-solid state. By dispersing clay mineral particles in water, the viscosity of the medium (water) is greatly increased. Thus, when excipients are prepared in a liquid or semi-solid form, both dispersing and anticaking agents are used to prevent drastic changes in dispersion properties.

Dilute smectite dispersions (smectite content <1% w/v) generally show Newtonian flow behaviour (Vali and Bachman, 1988; Lagaly,

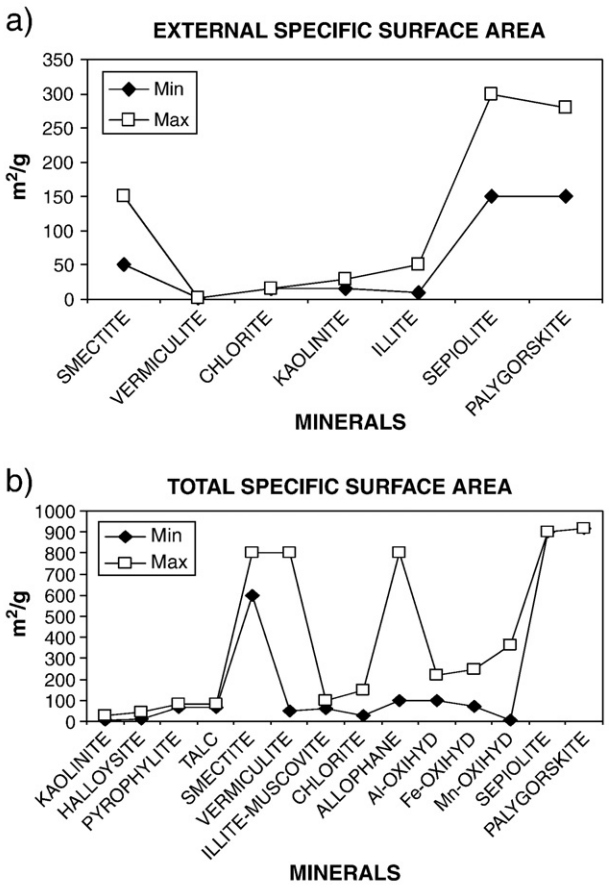

Fig. 2. a) External specific surface areas measured by adsorption of N_2 (BET) of representative clay minerals. Source: Carretero and Pozo (2007). b) Total (external and interlayer space) specific surface areas of different clay minerals and metal (hydr)oxides, measured by adsorption of polar organic compounds. Sources: Sparks (2005), Carretero and Pozo (2007).

2006). At concentrations >1% w/v, the flow behaviour of smectite dispersions becomes non-Newtonian, while the apparent viscosity increases exponentially with clay concentration. The flow of smectite dispersions is also influenced by the pH and ionic strength of the medium, as do the rate and mechanism of coagulation. Gelation represents an advanced stage of coagulation. Increasing time gels may regain their fluidity on applying mechanical stress (stirring or shearing). This process is known as thixotropy (Mewis, 1979). As the name suggests, 'antithixotropy' (rheopexy) is the reverse of thixotropy. A rheopexic dispersion shows a gradual rise in viscosity as time increases, and eventually transforms irreversibly into a gel state.

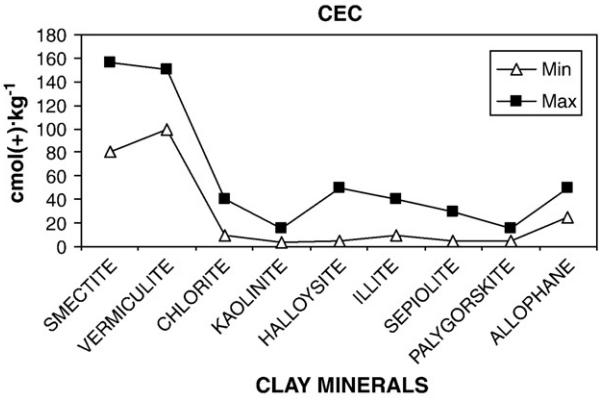

Fig. 3. Cation exchange capacity (CEC) of common clay minerals. Source: Grim (1968).