Multifaceted role of clay minerals in pharmaceuticals

The desirable physical and physiochemical properties of clay minerals have led them to play a substantial role in pharmaceutical formulations. Clay minerals like kaolin, smectite and palygorskite-sepiolite are among the world’s most valuable industrial minerals and of considerable importance. The elemental features of clay minerals which caused them to be used in pharmaceutical formulations are high specific area, sorption capacity, favorable rheological properties, chemical inertness, swelling capacity, reactivity to acids and inconsiderable toxicity. Of course, these are highly cost effectual. This special report on clay minerals provides a bird’s eye view of the chemical composition and structure of these minerals and their influence on the release properties of active medicinal agents. Endeavor has been made to rope in myriad applications depicting the wide acceptability of these clay minerals.

With a variegated range of physical, chemical and physicochemical properties, clay minerals have an undisputable role in pharmaceutical industries. The minerals employed primarily are oxides, carbonates, sulphates, chlorides, hydroxides, sulphides, phosphates, nitrates, borates and phyllosilicates. These are widely put into use owing to their unique features. The significant contributions of these minerals are in therapeutic, cosmetics and as bulk forming agents. These are biologically compatible and hence ensure the genesis of safe and effective drug delivery systems.

Keywords: clay minerals • drug delivery • kaolinite • pharmaceuticals • phyllosilicates

Clay, a group of natural minerals with plastic properties are primarily composed of hydrous-layer silicates of aluminium, occasionally containing magnesium and iron particles of smaller size, in other words, less than 2 μm (7.9 × 10⁻⁵ inch). Hence, in broader terms, clay minerals practically involve minerals of the above-cited particles size. These are essentially composed of silica, alumina, magnesia, iron and water with varying degree of potassium, sodium and calcium [1].

Besides clay minerals no other minerals quite as immensely attract pharma people. Since the 19th century clay minerals have been explored on the geological, geotechnical and mineralogical fronts; their myriad therapeutic aspects were highlighted primarily in the pharmaceutical research. Clay minerals are a class of phyllosilicates which usually form as a result of chemical weathering of silicate minerals at the surface of the Earth [2]. Clay minerals are widely used in the pharmaceutical industry as lubricants, desiccants, disintegrants, diluents, binders, pigments and opacifiers. The other vital uses are as emulsifying, thickening, isotonic and anticaking agents. These also serve as flavor correctors and carriers of active ingredients. Other unique features are dispersivity, hygroscopicity, unctuosity, thixotropy and their rendering a slightly alkaline reaction as pH is slightly more than 7, plasticity, opacity and various high-quality colors [3].
Clay minerals are primarily of a fine-grained natural material with particle size <2 μm. The physical and chemical properties of a particular clay mineral are dependent on its structure and composition. The structure and composition of the major industrial clays, in other words, kaolins, smectites and palygorskite–sepiolite, are very different even though each is comprised of octahedral and tetrahedral sheets as their basic building blocks. However, the arrangement and composition of the octahedral and tetrahedral sheets, as depicted in Figure 1, account for most differences in their physical and chemical properties. Clay minerals are stacked, polymeric sandwiches of tetrahedral and octahedral sheet structures. They are classified first into ‘layer types,’ differentiated by the number of tetrahedral and octahedral sheets that have combined, and then into ‘groups,’ differentiated by the kinds of isomorphic cation substitution that have occurred.

Clay minerals can be classified into seven groups as illustrated in Figure 2. Thus, mineral products for pharmaceutical use vary according to composition, crystallinity, habit and texture, greatly affecting their properties. The individual layers of clay minerals are composed of two, three or four sheets. The sheets are formed either by tetrahedrons [SiO₄]⁴⁻, abbreviated as ‘T’ or by octahedrons, for example, [AlO₃(OH)]⁶⁻, abbreviated as ‘O.’ The interior of tetrahedrons and octahedrons contain smaller metal cations, their apices being occupied by oxygen, which are with protons (as OH). All these fundamental structural elements are arranged to form a hexagonal network in each sheet.

Clay minerals with very fine, thin particles and high adsorbent properties are quite useful for the antibiotics sorption. Kim et al. studied the sorption of oxytetracycline on clay minerals especially in acidic soils with high organic matter content. The adsorption of four widely used drugs, carbamazepine, diclofenac, ibuprofen and ketoprofen, was investigated onto a porous
silica under varied ionic strengths, and with different anions, valent cations (Ca$^{2+}$ and Mg$^{2+}$), trivalent cations (Al$^{3+}$ and Fe$^{3+}$) and natural organic matter. The studies demonstrated that at a given pH the adsorption was most affected by ionic strength, trivalent cations and properties of pharmaceuticals. The increase of ionic strength resulted in an increase in the adsorption of carbamazepine [11]. Cation exchange was the major mechanism of ciprofloxacin desorption from clay mineral surface. Ciprofloxacin desorption from kaolinite and montmorillonite was investigated under different pHs, different concentrations of metal cations of various valencies (Na$^+$, Ca$^{2+}$ and Al$^{3+}$) and a cationic surfactant hexadecyl trimethylammonium (HDTMA), with different desorption cycles [12]. Enhanced desorption hysteresis of carbamazepine was observed for the smectites with negatively charged sites compensated with inorganic cations such as K$^+$, Ca$^{2+}$ and NH$_4^+$ than the desorption from organic cation-modified smectites (e.g., HDTMA clay), suggesting that the intercalated carbamazepine molecules are more resistant to release than carbamazepine partitioning in alkyl organic phase [2]. In addition, the large cation exchange capacity and surface area make the clay a good candidate to remove cationic pharmaceuticals from the effluent of waste water treatment facilities [13]. The protein adsorption capacity and selectivity of kaolinite and metakaolinite show a clear dependence on the chemical nature of the adsorbents surface and on the textural properties. Kaolinite and metakaolinite exhibit a very high affinity and good retention capacity for proteins like bovine serum albumin specially A-LA and B-LG [14]. The clay/poly(N-isopropylacrylamide) (PNIPAm) nanocomposite hydrogels, using lithium magnesium silicate hydrate as a clay mineral physical cross-linker were prepared to remove crystal violet from aqueous solution [15]. Similarly, Ballav and associates studied the absorption behavior of polypyrrole-coated halloysite nanotube nanocomposite [16]. Recently, clays have been modified through several approaches like conventional ion exchange reactions, sol-gel linking, atom transfer radical polymerization and polymer intercalation. The organic interaction incorporates different noncovalent bonding forces, such as amido acid five-membered ring chelation, carboxylic acid chelation, intermolecular hydrogen bonding and double-layer hydrophobic alignment in a layered clay confinement. Furthermore, the layered structure could be totally exfoliated and structurally randomized into individual silicate platelets using different mechanisms, such as the phase inversion of amphiphilic copolymer emulsifiers and phase transitions that involve zigzag Mannich polyamides. Different intercalation and exfoliation strategies help

| Group          | Octahedral character | Chemical formula | Al$_2$Si$_4$O$_8$·(OH)$_4$ | Al$_2$Si$_4$O$_8$·(OH)$_2$ | Si$_8$O$_4$(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ |
|----------------|---------------------|------------------|----------------------------|----------------------------|--------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Kaolinite-serpentine | Two-sheet phyllosilicates, where the T:O ratio = 1:1 and the charge of the two-sheet layer = 0 | Al$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Si$_8$O$_4$(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ | Mg$_3$Si$_4$O$_8$·(OH)$_2$ |
| Group | Pharmaceutical activity | Mechanism of action                                                                 | Ref. |
|-------|--------------------------|--------------------------------------------------------------------------------------|------|
| Palygorskite-sepiolite, smectites | Gastric and duodenal ulcer | H⁺ neutralizing capacity decomposition in gastric acid and bring the bowel pH to 6   | [24] |
| Kaolinite, palygorskite-sepiolite, smectites | Gastrointestinal protector | High-specific area and sorption capacity                                              | [25] |
| Palygorskite-sepiolite, smectites kaolinite | Antidiarrhoeics | Astringent action of the Ca²⁺ ion, which forms nonsoluble, hydrated phosphates        | [26] |
| Kaolinite-talc, smectites | Dermatological protectors | Adhere to skin, forming a film that mechanically protects the skin. Adsorbs the skin’s secretions, and creates a large surface for their evaporation which promotes a gentle antiseptic action by producing a water poor medium that is unfavorable for the development of bacteria | [27] |
| Mirabilite, epsomite, periclase brucite, magnesite | Laxatives | High solubility in water and HCl; release of Na⁺ or Mg²⁺ ions and nontoxic anions when ingested | [28] |
| Kaolinite | Anti-inflammatories and local anesthetics | High absorption and heat retention capacities                                           | [19] |
| Palygorskite, sepiolite, kaolinite, smectites, talc | Cosmetic creams, powders and emulsions | Opacity and high sorption capacity                                                    | [29] |
| Silver and cationic surfactant-modified smectites | Antibacterial activity | Heavy metals modified montmorillonites exhibit high cation exchange capacity, large specific surface and colloid properties that give rise to optimum adsorbents of organic and inorganic substances | [30] |
| Halite, sylvite, melanterite, epsomite, mirabilite | Homeostatics | Smectite group of minerals have wider applications due to their high swelling and cation exchange capacity | [28] |
## Multifaceted role of clay minerals in pharmaceuticals

### Special Report

| Type of drug-delivery system | Natural minerals employed | Mechanism                                                                                                                                                                                                 | Ref.                      |
|-----------------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Extended release systems    | Smectites montmorillonite fibrous minerals Hydrotalcite | They can retain large amounts of drug due to their high cation exchange capacity                                                                                                                             | [31–38]                   |
| Targeted delivery systems   | Natural, synthetic, nanocomposites clay-polymers, films and hidrogels composites clay-polymers | Interact with drugs reducing their absorption. Therefore, such interactions can be used to achieve technological and biopharmaceutical advantages, regarding the control of release. | [39]                      |
| Colon delivery systems      | Montmorillonite          | Pharmaceutical natural minerals and drug interactions                                                                                                                                                     | [40,41]                   |
| Periodontal systems         | Laminar minerals         | Improved bioadhesion                                                                                                                                                                                      | [42,43]                   |
| Hydration-activated extended release systems | Smectites                         | Act as disintegrant agents in tablet formulations because of their hydrophilic and swelling properties                                                                                               | [44–46]                   |
| Microparticles              | Amorphous silica bentonite attapulgite kaolin talc | Encapsulation of surface, precipitation inclusion and pharmaceutical natural minerals–polymer interaction                                                                                        | [47–50]                   |
| Nanoparticles               | Halloysite montmorillonites Bentonite porous silica | Pharmaceutical natural minerals provide spontaneous submicron dispersions in aqueous media, resulting in low cost and biocompatible systems with large surface area and high-inclusion capacity | [16,22,51]                |
| Encapsulation of drugs inside layered double hydroxides (LDHs) with Mg^{2+}, Al^{3+}, and Fe^{3+} in the layers | Hydrotalcite | Hydrotalcite-layered solids with positively charged layers and charge-balancing anions in the interlayer space which protects drugs like nonsteroidal anti-inflammatory drugs in the GI tract | [52]                      |
| Cellular uptake             | Hydrotalcite-derived antacidic and antipeptic formulations | Layered double hydroxides as nonviral vectors for delivery of antisense oligonucleotides                                                                                                               | [53]                      |
| Silver nanoparticles and multiwalled carbon nanotubes | Montmorillonite | Transfection studies of these various functionalized nanopreparations implied that the gene delivery vector based on silver nanoparticles stabilized with starch and montmorillonite were more promising | [54]                      |
in developing detailed understanding of clay chemistry, thus exploring wider horizons of clay applications [17].

Clay minerals sorption activity is the most suitable application in veterinary science. Kaolins and smectites are most commonly used in animal nutrition as growth promoters and supplements for the treatment of gastrointestinal disturbances, particularly diarrhea [18].

The antibacterial activity of silver and cationic surfactant modified smectites from North Patagonia, Argentina, were tested in growth inhibition of Escherichia coli bacteria by the test of susceptibility on solid medium [19]. Minerals also enjoy diagnostic, odontological and traumatological applications, and are used in spas and aesthetic centers for therapeutic proposes [20]. Research focused on the role of clay minerals in kerogen formation, kerogen conversion to petroleum, oil migration and entrapment in reservoirs identify significant interactions arising from the adsorptive and catalytic properties of clay minerals and structural changes during diagenetic transformations [21]. Recently, Das et al., 2014 explored the significant antibacterial activity of copper nanoparticle-decorated organically with modified montmorillonite/epoxy nanocomposites against ubiquitous Gram-negative bacteria Klebsiella pneumonia and Gram-positive bacteria Staphylococcus aureus [22].

Kaolinite, talc, palygorskite and smectites are used for therapeutic purposes in pharmaceutical formulations as active principles or excipients. The possible use of sepiolite as active principle or excipient in pharmaceutical formulations was also investigated. Kaolinite, talc, palygorskite and smectites are used as excipients in cosmetics and pharmaceutical preparations [23]. A summary of the pharmacological activities of the clay minerals is described in Table 2. They also have an admirable role in the targeted and modified drug delivery system as in Table 3.

**Conclusion & future perspective**

Research trends on clay minerals are heading toward the synthesis of minerals based on atomic and molecular scale design by affecting their physicochemical properties and thus they have a wide scope of applications in pharmaceutics. Chemical and physical interactions of clays with water and many other chemical species, and their dynamics, offer further scope. Biological implications related to clays are likely to be investigated more extensively. Novel materials based on nanotechnology, biochemical and medical applications, and environmental aspects are envisaged [55]. Chemically modified clay mineral electrodes are also being explored for many chemical sensor applications. Tuning the process and coupling it with a separation technique can achieve effective DNA quantification. Because of the stability of clays, combining them with enzymes and suitable redox mediators — for example, clay in conjunction with hydroquinone mediator — could be a new way to quantify microbiological systems such as fungi and bacteria such as Escherichia coli [56]. Novel-layered nanohybrid materials with controlled functions and microstructures are also being extensively explored. Nanocomposites based on clays and organic compounds are expanding. Studies of domain structures in layer silicates will continue, and further refinements in mixed-layer structure analysis can be expected. The study of clay mineral synthesis and alteration in nature shows signs of important reactivation. Furthermore, the self-assembled film of clay minerals has a highly regular multilayered nanostructure over a large area and could appreciably entrap in between the volume of air [57]. The combination of regular structure and substantial air volume contributes to the low thermal conductivity and flame blocking property of the film.

Clay-organic studies are developing in many directions. An understanding of the surface chemistry, particle shape and relative size distribution are crucial in developing such materials for an increasingly demanding and diverse world [58]. Organo-clays receive great interest for applications based on their capacity for selective adsorption of molecules. Thus, they have been used for application in chromatography separations, to remove organic pollutants from air and water, and to develop improved formulation for pesticides, as chemical sensor and molecular sieves, and so on. Among other properties applications based on special structural, gas barrier, antiflammability or others can be mentioned. Interesting photochemical behavior may also arise from the specific structure of those nanocomposites. Depending on the layer structure and specific properties, such as high-specific surface area, ion exchange capacity or hydration property, clay minerals are widely used in pharmaceuticals, and as adsorbents, catalysts or catalyst supports, ion exchangers and decolorizing agents.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

**Open Access**

This work is licensed under the Creative Commons Attribution 4.0 License. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/
Multifaceted role of clay minerals in pharmaceuticals

Special Report

Executive summary

Unique features of clay minerals in pharmaceutical industry

- The enormous surface area, surface chemistry and surface charge impart significant and unique physical properties to the clay minerals, owing to which these possess tremendous scope to be utilized as therapeutic, cosmetics, functional, inert and bulk agents.
- Most commonly employed clay minerals in pharmaceuticals and cosmetics are kaolinite, talc, montmorillonite, saponite, hectorite, palygorskite and sepiolite.
- Precisely clay minerals serve as lubricants, desiccants, disintegrants, diluents, binders, pigments and opacifiers. The other imperative one are emulsifying, thickening, isotonic and antisking agents.
- The predominant curative properties include antacids, gastrointestinal protectors, antidiarrheics, laxatives, homeostatics, emetics, antiinflammatories and so on.

References

Papers of special note have been highlighted as:
• of interest; • of considerable interest

1 Grim RE. Clay minerals. Encyclopedia Britannica. http://www.britannica.com/EBchecked/topic/120723/clay-mineral
2 Zhang W, Ding Y, Boyd SA, Teppen BJ, Li H. Sorption and desorption of carbamazepine from water by smectite clays. Chemosphere 81, 954–960 (2010).
3 Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical industry: Part I. Excipients and medical applications. Appl. Clay Sci. 46, 73–80 (2009).
4 Guggenheim S, Adams JM, Bain DC et al. Summary of recommendations of nomenclature committees relevant to clay mineralogy: report of the Association Internationale pour l’Etude des Argiles (AIPEA) Nomenclature Committee for 2006. Clay Minerals 41, 863–877 (2006).
5 Murray HH. Applied Clay Mineralogy – Occurrences, Processing and Application of Kaolins, Bentonites, Palygorskite-Sepiolite, and Common Clays.141–145 (2006).
6 Spósito G, Skipper NT, Sutton R, Park SH, Soper AK, Greathouse JA. Surface geochemistry of the clay minerals. Proc. Natl Acad. Sci. USA 96, 3358–3364 (1999).
7 Liu H, Shen T, Li T, Yuan P, Shi G, Bao X. Green synthesis of zeolites from a natural aluminosilicate mineral rctorite: effects of thermal treatment temperature. Appl. Clay Sci. 90, 53–60 (2014).
8 Viseras C, Lopez-Galindo A. Pharmaceutical applications of some spanish clays _sepiolite, palygorskite, bentonite_: some preformulation studies. Appl. Clay Sci. 14, 69–82 (1999).
9 Konta J. Clay and man: clay raw materials in the service of man. Appl. Clay Sci. 10, 275–335 (1995).
10 Kim YK, Lim SJ, Han MH, Cho JY. Sorption characteristics of oxytetracycline, amoxicillin, and sulfathiazole in two different soil types. Geoderma 185, 97–101 (2012).
11 Bui TX, Choi H. Influence of ionic strength, anions, cations, and natural organic matter on the adsorption of pharmaceuticals to silica. Chemosphere 80, 681–686 (2010).

Highlights of the role of clay minerals in therapeutics.

12 Wu LM, Zhou CH, Keeling J, Tong DS, Yu WH. Towards an understanding of the role of clay minerals in crude oil formation, migration and accumulation. Earth Sci. Rev. 115, 373–386 (2012).
13 Zhao Hui L, Chang PH, Jiang WT, Jean JS, Hong H, Liao L. Removal of diphenhydramine from water by swelling clay minerals. J. Colloid Interface Sci. 360, 227–232 (2011).
14 Durante-Silva R, Villa-García MA, Rendueles M, Díaz M. Structural, textural and protein adsorption properties of kaolinite and surface modified kaolinite adsorbents. Appl. Clay Sci. 90, 73–80 (2014).
15 Zhang Q, Zhang T, He T, Chen L. Removal of crystal violet by clay/ PNiP Am nanocomposite hydrogels with various clay contents. Appl. Clay Sci. 90, 1–5 (2014).
16 Ballav N, Choi HJ, Mishra SB, Maity A. Polypyrrole-coated halloysite nanotube clay nanocomposite: synthesis, characterization and Cr (VI) adsorption behaviour. Appl. Clay Sci. 102, 60–70 (2014).
17 Wang YC, Huang TK, Tung SH, Wu TM, Lin JJ. Self-assembled clay films with a platelet–void multilayered nanostructure and flame-blocking properties. Sci. Rep. 3, 2621 (2013).
18 Slamova R, Trekova M, Vondruskova H, Zraly Z, Pavlik I. Clay minerals in animal nutrition. Appl. Clay Sci. 51, 395–398 (2011).
19 Parolo ME, Fernández LG, Zajenkovsky I, Sánchez MP, Baschini M. Science against microbial pathogens: communicating current research and technological advances. In: Antibacterial Activity of Materials Synthesized from Clay Minerals. Vilas AM (Ed.). FORMATEX, 144–151 (2011). http://www.formatex.info/microbiology3/book/144–151.pdf
20 Viseras C, Aguetti C, Cerezo P, Lopez-Galindo A. Uses of clay minerals in semisolid health care and therapeutic products. Appl. Clay Sci. 36, 37–50 (2007).

Basics of clay minerals.

1 Grim RE. Clay minerals. Encyclopedia Britannica. http://www.britannica.com/EBchecked/topic/120723/clay-mineral
2 Zhang W, Ding Y, Boyd SA, Teppen BJ, Li H. Sorption and desorption of carbamazepine from water by smectite clays. Chemosphere 81, 954–960 (2010).
3 Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical industry: Part I. Excipients and medical applications. Appl. Clay Sci. 46, 73–80 (2009).
4 Guggenheim S, Adams JM, Bain DC et al. Summary of recommendations of nomenclature committees relevant to clay mineralogy: report of the Association Internationale pour l’Etude des Argiles (AIPEA) Nomenclature Committee for 2006. Clay Minerals 41, 863–877 (2006).
5 Murray HH. Applied Clay Mineralogy – Occurrences, Processing and Application of Kaolins, Bentonites, Palygorskite-Sepiolite, and Common Clays.141–145 (2006).
6 Spósito G, Skipper NT, Sutton R, Park SH, Soper AK, Greathouse JA. Surface geochemistry of the clay minerals. Proc. Natl Acad. Sci. USA 96, 3358–3364 (1999).
7 Liu H, Shen T, Li T, Yuan P, Shi G, Bao X. Green synthesis of zeolites from a natural aluminosilicate mineral rctorite: effects of thermal treatment temperature. Appl. Clay Sci. 90, 53–60 (2014).
8 Viseras C, Lopez-Galindo A. Pharmaceutical applications of some spanish clays _sepiolite, palygorskite, bentonite_: some preformulation studies. Appl. Clay Sci. 14, 69–82 (1999).
9 Konta J. Clay and man: clay raw materials in the service of man. Appl. Clay Sci. 10, 275–335 (1995).
10 Kim YK, Lim SJ, Han MH, Cho JY. Sorption characteristics of oxytetracycline, amoxicillin, and sulfathiazole in two different soil types. Geoderma 185, 97–101 (2012).
11 Bui TX, Choi H. Influence of ionic strength, anions, cations, and natural organic matter on the adsorption of pharmaceuticals to silica. Chemosphere 80, 681–686 (2010).

Basics of clay minerals.
• Basics of clay minerals.

26 Murray HH. Traditional and new applications for kaolin, smectite, and palygorskite: a general overview. Appl. Clay Sci. 17, 207–221 (2000).

• Basics of clay minerals.

27 Arab S, Alshikh A. The use of Clay Minerals of the Dead Sea as Drugs. In: Clay Minerals (Volume 5). Murray HH (Ed), NY, USA 5, 112-115 (2012).

28 Silva PSC, Oliveira SMB, Farias L, Fávaro DIT, Mazzilli BP. Chemical and radiological characterization of clay minerals used in pharmaceutics and cosmetics. Appl. Clay Sci. 52, 145–149 (2011).

29 Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical and cosmetic industries Part II. Active ingredients. Appl. Clay Sci. 47, 171–181 (2010).

• Highlights the role of clay minerals in pharmaceutical sciences.

30 Williams LB, Haydel SE. Evaluation of the medicinal use of clay minerals as antibacterial agents. Int. Geol. Rev. 52, 745–770 (2010).

31 Maheshwari RK, Sharma SN, Jain NK. Adsorption studies of phenformin hydrochloride on some clays and its application in formulating sustained release dosage forms. Ind. J. Pharm. Sci. 50, 101–105 (1988).

32 Forni F, Iannuccelli V, Cameroni R, Coppi G, Bernabei MT. Swellable heterogeneous matrices: physical properties and release mechanisms. Farmaco Prat. 41, 155–164 (1986).

33 Forni F, Iannuccelli V, Coppi G, Bernabei MT. Effect of montmorillonite on drug release from polymeric matrices. Arch. Pharm. 322, 789–793 (1989).

34 Aguzzi C, Viseras C, Cerezo P, Rossi S, Ferrari F, Caramella C. Control of tetracyclines delivery by their interaction with veegum. In: Proceedings of the 30th Annual Meeting & Exposition of the Controlled Release Society, 19–23 July (Glasgow, Scotland, UK (2003). Abstract 730).

35 Aguzzi C, Viseras C, Cruz J, Zafra M, Cerezo P, Rossi S. Development of new controlled release systems based on mineral supports: III. Release studies of tetracyclines–silicate interaction products. Proceedings Of The 1st Enfespo Conference On Optimising Drug Delivery And Formulation: New Challenges In Drug Delivery. Acta del Congreso, Versailles, 136–137 (2003).

36 Cerezo P. Mecanismos Y Cineticas De Adsuccion-Liberacion De Farmacos En Sistemas de Liberacion Controles. Contribucion Al Estudio De Vehiculos y Sistemas de Liberacion de Fármacos. University of Granada, Granada (E), PhD thesis] (2005).

37 Ambrogi V, Fardella G, Grandolini G, Perioli L. Intercalation compounds of hydrotricate-like anionic clays with anti-inflammatory agents. I. Intercalation and in release of ibuprofen. Int. J. Pharm. 220, 23–32 (2001).

38 Ambrogi V, Fardella G, Grandolini G, Perioli L, Tirali HC. Intercalation compounds of hydrotricate-like anionic clays with anti-inflammatory agents. II. Uptake of diclofenac for a controlled release formulation. AAPS PharmSci Tech. 3, E26 (2002).

39 Rodrigues LA A, Veiga F, de Freitas RM et al. The systems containing clays and clay minerals from modified drug release: a review. Colloids Surf. B Biointerfaces 103, 642–651 (2013).

• Highlights the role of clay minerals in drug delivery.

40 Shirivastava R, Jain SR, Frank SG. Dissolution dialysis studies of metronidazole–montmorillonite adsorbates. J. Pharm. Sci. 74, 214–216 (1985).

41 Lin FH, Lee YH, Jian CH. A study of purified montmorillonite intercalated with 5-fluorouracil as drug carrier. Biomaterials 23, 1981–1987 (2002).

42 Aguzzi C, Ferrari F, Gatti A, Rossi S, Bonferoni MC, Cerezo P. Novel controlled release formulations based on tetracycline–clay interaction products for periodontal administration. Proceedings of the 45th Simposio AFI. Rimini Italy (2005), 177

43 Aguzzi C, Ferrari F, Cerezo P, Rossi S, Bonferoni MC, Dacarro C. Suitability assessment of tetracycline-loaded clays in the treatment of periodontitis. Proceedings of the 1st PharmSciFair, Pharmaceutical Sciences Fair and Exhibition. NICE, France PO-258 (2005).

44 Wai KN, Banker GS. Some physicochemical properties of the montmorillonites. J. Pharm. Sci. 55, 1215–1220 (1966).

45 Fielden KE. US5556639 (1996).

46 Viseras MT, Aguzzi C, Cerezo P, Viseras C, Lopez-Galindo A, Valenzuela C. Study of adsorption kinetics of 5-aminosalicylic acid in phyllosilicates for controlled drug delivery in the treatment of inflammatory bowel disease. Pharmaceutical Sciences Fair and Exhibition. Nice, France, PO-253 (2005).

47 Zhu Y, Adjei AL. US2002110527 (2002).

48 Price RR, Gaber BP, Iwov Y. In vitro release characteristics of tetracycline HCl, khellin and nicotinamide adenine dinucleotide from halloysite; a cylindrical mineral. J. Microencapsul. 18, 713–722 (2001).

49 Byrne R S, Deasy PB. Use of porous aluminosilicate pellets for drug delivery. J. Microencapsul. 22, 423–437 (2005).

50 Levis SR, Deasy PB. Use of coated microtubular halloysite for the sustained release of hydrochloride and propranolol hydrochloride. Int. J. Pharm. 253, 145–157 (2003).

51 Lopez-Galindo A, Viseras C, Cerezo P. Compositional, technical and safety specifications of clays to be used as pharmaceutical and cosmetic products. Appl. Clay Sci. 36, 51–63 (2007).

52 Arcino MD, Fernández A, Martín C, Rives V. Release studies of different NSAIDs encapsulated in Mg,Al,Fe-hydrotracites. Appl. Clay Sci. 42, 538–544 (2009).
**Multifaceted role of clay minerals in pharmaceuticals**

**Special Report**

53 Choy JH, Choi SJ, Oh JM, Park T. Clay minerals and layered double hydroxides for novel biological applications. *Appl. Clay Sci.* 36, 122–132 (2007).

54 Sironmani TA. Comparison of nanocarriers for gene delivery and nanosensing using montmorillonite, silver nanoparticles and multiwalled carbon nanotubes. *Appl. Clay Sci.* 103, 55–61 (2015).

55 Liu P. Polymer modified clay minerals: A review. *Appl. Clay Sci.* 38, 64–76 (2007).

56 Guggenheim S, Adams JM, Bain DC et al. Summary of recommendations of nomenclature committees relevant to clay mineralogy: report of the Association Internationale pour l’Etude des Argiles (AIPEA) Nomenclature Committee for 2006. *Clay Minerals* 41, 863–877 (2006).

- Basics of clay minerals.

57 Chiu C, Huang T, Wang Y, Alamani B, Lin JJ. Intercalation strategies in clay/polymer hybrids. *Prog. Polymer Sci.* 39, 443–485 (3). (2014).

58 Sposito G, Skipper NT, Sutton R, Park SH, Soper AK, Greathouse JA. Surface geochemistry of the clay minerals. *Proc. Natl Acad. Sci. USA* 96, 3358–3364 (1999).