

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Multifunctional Clay in Pharmaceuticals

*Nandakumar Selvasudha,
Unnikrishnan-Meenakshi Dhanalekshmi,
Sekar Krishnaraj, Yogeewarakannan Harish Sundar,
Nagarajan Sri Durga Devi and Irisappan Sarathchandiran*

Abstract

Clay has its widespread applications in pharmaceuticals from ancient world to modern era. It is one of the excellent excipients present in the commercially available pharmaceuticals. Its use in many of dosage forms viz. in suspension, emulsion, ointments, gels, tablet and as drug delivery carrier as suspending agent, emulsifying agent, stiffening agent, binder, diluent, opacifier, and as release retardant have been explored in many studies. Variety of minerals is used as both excipient and as an active ingredient; among that kaolinite, talc, and gypsum are important. Their inertness, low toxicity, versatile physiochemical properties and cost effectiveness has increased its usage in pharma industries. Many minerals have its own pharmacological action as antacid, anti-bacterial, anti-emetic, anti-diarrheal agent and as skin protectant etc. Their unique structure which helps them to absorb material onto their layered sheets has opened a wide variety of applications in drug delivery. The understanding of surface chemistry and particle size distribution of clay minerals has led the pharmaceutical field in many directions and future perspectives.

Keywords: pharmaceuticals, active pharmaceutical ingredient, excipients, inherent medicinal properties, drug delivery carrier, synergistic effect

1. Introduction

Usage of clay in medicine dates back to prehistorian era. Their evidences are present throughout the history from the clay pots of Nippur, Mesopotamia which gave the evidence of using clay against hemorrhages, the book “papyrus ebers” dating back in 1600 BC provided the details of using clay-based medicine for certain diseases. Many vital information on medical clay is mentioned in “On Airs, Waters and Places” written by Hippocrates (460–377 BC). One of the notable healing clay used in medicine during early days is known as Armenian bole (*bolus armenus*). They are pharmacologically used for the treatment of diarrhea, dysentery, hemorrhage, even as an astringent in few cases. Avicenna in his book “El Canon” classified various types of clay and their internal and external applications. He also mentioned their role in anti-poison treatment and rheumatic disorders. Even though their consumption has been subjected to lot of questions the practice of using medicinal and edible clay prevails till date for their curative and beneficial effects.

Their usage in pharmaceutical industry is invariable due to their versatile property; they are used in almost every formulation like tropical to oral and also as an excipient. As the scientific community grows, there have been many papers published to support the medicinal and curative benefits of clay minerals [1–8].

The important component of clay is the clay minerals but it also comprises of associated minerals, organic, and inorganic materials. Clay can be grouped based on the geological aspects such as

- Primary or residual clay
- Secondary or sedimentary clay
- Special clay
- Common clay
- Refractory clay
- Nano clay
- Modified clay

Each clay has their own properties to distinguish themselves from the other. The classification also extends based on their geometrical shape, arrangement, and their usage. The classifications are given below.

Based on the geometry of the clay, it has been classified into four major groups and the subgroups are specified in **Table 1**.

1. Kaolinite
2. Smectite
3. Illite
4. Chlorite

The variation is due to the arrangement of tetrahedral and octahedral sheets, where kaolinite group has one tetrahedral sheet arranged over one octahedral sheet

S. No	General formula	Group	Layer type
1	$\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})$	Kaolinite-Serpentine	1:1
2	$\text{Al}_2\text{Si}_4\text{O}_{10}(\text{OH})_2\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$	Pyrophyllite-talc	2:1
3	Montmorillonate $(\text{Al}_{1.67}\text{Mg}_{0.33})\text{Si}_4\text{O}_{10}(\text{OH})_{2M+0.33}$ Saponite: $\text{Mg}_3(\text{Si}_{3.67}\text{Al}_{0.33})\text{O}_{10}(\text{OH})_{2M+0.33}$ Hectorite $(\text{MgLi})_3(\text{SiAl})_4\text{O}_{10}(\text{OH})_{2M+}$	Smectite	2:1
4	$(\text{Mg,Fe,Al})_3(\text{Al,Si})_4\text{O}_{10}(\text{OH})_{2.4}\text{H}_2\text{O}$	Vermiculite	2:1
5	$\text{KAl}_2(\text{Si}_3\text{Al})\text{O}_{10}(\text{OH})_2$	Mica/Illite	2:1
6	$\text{Al}_4[\text{Si}_8\text{O}_{20}](\text{OH})_4\text{Al}_4(\text{OH})_{12}$	Chlorite	2:1:1
7	$(\text{Mg,AL,Fe}^{3+})_5(\text{Si,Al})_8\text{O}_{20}(\text{OH})_2(\text{OH}_2)_{4.4}\text{H}_2\text{O}$ $\text{Mg}_8\text{Si}_{12}\text{O}_{30}(\text{OH})_4(\text{OH}_2)_{4.8}\text{H}_2\text{O}$	Palygorskite-sepiolite group	

Table 1.
Subgroups of the clay.

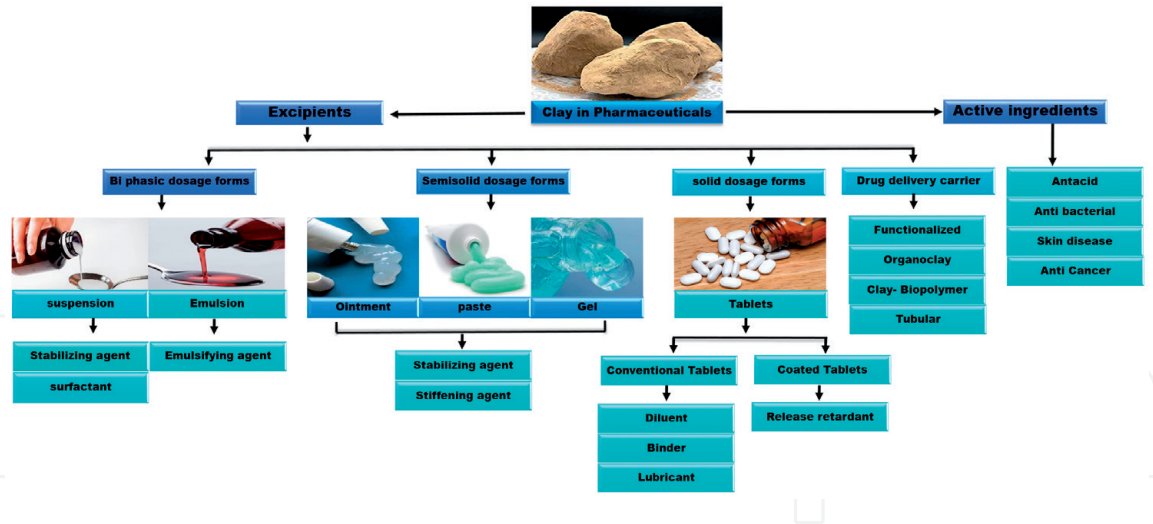


Figure 1.
Classification and usage of clay minerals.

whereas two tetrahedral sheets arranged over one octahedral sheet in smectite group. In case of chlorite group, octahedral sheet is arranged adjacent to 2:1 layer. The clay minerals exhibit versatile properties such as high adsorption capacity, chemical inertness, thixotropy, specific surface area, ion exchange capacity, less toxicity for oral administration, swelling property justifying their wide applications in pharmaceutical industries as excipient to enhance the physiochemical and organoleptic characteristics of a drug. It also helps in aiding drug conservation, elaboration, liberation of drug into the organism. These are achieved by incorporating the clay minerals such as disintegrates, lubricants, opacifiers, binders, diluents, isotonic agent, anti-caking agents, emulsifying agent, desiccant, thickening agent, and flavor modulators. Apart from the pharmaceutical applications, clay minerals also possess a lot of pharmacological properties like anti-bacterial, anti-viral, anti-diarrheal, gastro-intestinal protector, skin protection, and a potent detoxifier. The future trend holds for the MDDS using nano-clay minerals due to their inertness and biocompatibility. More details about the pharmaceutical and pharmacological uses of clay minerals and their advancement in drug delivery system have been discussed in the following sections. Further the classification and usage of clay minerals is illustrated in **Figure 1**.

2. Use of clay as excipients

An excipient is an inert additive ingredient formulated along with active compound to enhance its organoleptic, physiochemical properties. Clay has been used for almost every type of excipients (**Table 2**). Though several investigations showed that clay interacts with the drug molecule conversely to the nature of excipients, the interaction may hinder the drug bioavailability inside the body. The co-administration of montmorillonite leads to the degradation of certain cardiovascular tonic [9], anti-inflammatory drug [10]. Similarly, palygorskite and sepiolite degraded hydrocortisone and dexamethasone [11, 12]. Certain clay also affects the chemical stability of diazepam. Drugs such as phenobarbital sodium, diazepam solution, and lansoprazole show interaction with magnesite. Bioavailability of tetracycline, indomethacin, aspirin, aspartame, ampicillin, cephalixin, and erythromycin has been drastically affected by calcium rich minerals. Clay minerals has also shown tendency to affect the drug liberation by interacting with the drugs through various mechanisms. They have shown to affect the liberation of amphetamines, analgesics, antibiotics, anxiolytics, solar protectors, and anti-histamines [13–16]. The adsorption of anti-histamines, antibiotics, atropine

Type of Excipient	Clay minerals	Drug used
As Diluent	Kaolin, talc, sepiolite, smectite, Magnesite	Slim well tablet, Quantrim, Riclasip, Riboflavin hard gelatine capsule
As Binder	Gypsum, hydroxyapatite, kaolin	Kaolin-Eudragit 30 in many tablets
As Disintegrant	Palygorskite, kaolin, sepiolite	Hydrochlorothiazide
As Granulating agent	Kaolin, anhydrite, periclase	Granules of NaCl and kaolin in Tablets preparation
As Emulsifying and wetting agent	Kaolin, palygorskite, smectites, sylvite, halite	Sulfur ointments.
As Suspending agent	Kaolin, palygorskite, smectites, sylvite, halite	Toxiban, morphine suspensions
As Drug delivery carrier	Natural MMT Modified MMT Acid treated MMT MMT-Saponite Kaolinite pillared MMT Functionalized kaolinite Natural MMT-Biopolymer MMT-Chitosan MMT-Alginate MMT-Guar gum MMT-PLGA MMT-PLLA MMT-PLLA-PEG-PLLA Modified MMT-Biopolymer Organommodified MMT-PVP/PCL MMT-Saponite-Chitosan Kaolinite-PVP-Sodium laural sulphate Natural HNT Natural Palygorskite Natural sepiolite HNT-Biopolymer HNT-Chitosan HNT-Alginate HNT-PEG HNT-PVA Sepiolite-Chitosan	Diclofenac sodium, chlorhexidine, gallic acid, promethazine Ciprofloxacin, Ag-Nanoparticles of Tetracycline, gentamycin, theophylline, nitric oxide, acetyl salicylic acid, Ibuprofen Mesalazine, oxytetracycline Venlafaxine, olanzapine Ibuprofen Dexamethasone, atenolol 6-mercaptopurin Gemcitabine Naproxen, curcumin Nicotine 5-flurouracil Chlorhexidine 5-amino salicylic acid, binase, tetracycline, amoxicillin, paclifaxel Ofloxacin, isoniazid Carvacrol, praziquantel Doxorubicin, aspirin, curcumin, Vancomycin, 5-flurouracil, hydrocortisone Atorvastatin

Table 2.
Application of clay minerals as excipient.

sulfate, salicylate, hyoscyamine, hydrobromide, paracetamol, and chloroquine into periclase and brucite has been showed by Khalil et al. [15]. These interactions have been proven useful since they are used to retard drug release. So they aid in controlled drug release and improve the Tmax considerably.

2.1 Clay in biphasic liquid formulation

2.1.1 In suspension

Excipients are required in the biphasic system in order to obtain proper wetting and to maintain stability of the formulation. In order to overcome the

hydrophobicity of the drug and to aid in dispersion, clay minerals are added to the suspension as wetting agent. Sulfur ointment is prepared by blending kaolin with sulfur dispersed in oil phase [17]. The usage of bentonite as a wetting agent in foundation creams is also documented [18]. The clay also helps to maintain the stability by acting as suspending and anti-caking agent. They prevent sedimentation, changes in dispersion property, and flocculation. The criteria of selection of suitable suspending agent depend on compatibility, appearance, source, cost, and pH tolerance. The properties of the suspending agent including high viscosity at low shear rate, temperature, and storage tolerance, should not be affected by electrolyte or pH and be non-toxic. The formation of aggregates which in turn leads to the caking of solids would be the problem of suspension at the higher concentration. Reduction in the particle size or viscosity could not prevent caking. Caking can be prevented by flocculation and electrostatic stabilization [19, 20]. Kibbe showed that the increase in the stability of suspension using kaolin and talc as suspending and anti-caking agent. A suspension of pectin containing MAS dispersed in water along with kaolin under constant agitation at 70°C to which pectin was added, CMC was used to modify viscosity [17]. The usage of MAS and its four types (IA, IB, IC, and IIA) as a suspending agent has been commercialized and recognized by pharmacopeias, as they do not affect the pourability or spreadability of the suspension. Sarfaraz [17] reported the usage of magnabrite S (10 mg/ml) and magnabrite K (15 mg/ml) in bismuth sub-salicylate suspension in which smooth gel was obtained as a final product. The usage of MAS (veegum HV) as gelling agent was studied by Sarfaraz [17] and Vanderbilt report [21]. Vanderbilt report also suggested that the gelling property of veegum HV was affected by acids and improved by alkalies. An antacid suspension with veegum HV was prepared by Sarfaraz [17] using xanthan gum to modify viscosity. Schott [22] optimize the concentration of bentonite as suspending agent and concluded that the concentration between 0.5–5% w/v was suitable for formulations. Bismuth subnitrate suspension produces good flocculation at 1.7% w/v of bentonite.

Many semisolid formulations use phyllosilicate as suspending agent due to their good adsorptive capacity which can be further improved by heating [23]. In many semisolid topical formulations, surface activated kaolin is added to enhance the stability and water miscibility of hydrophobic drug. Pharmaceutical preparation such as kaolin and morphine oral suspension BP, Toxiban suspension use kaolin as suspending anti-caking agent. The effect of crystallinity of kaolin on aqueous suspensions was studied by Ndlovu et al. Due to their dominant negative charge and ability to create permanent electrostatic repulsion justify kaolin use in suspension. The effect of non-ionic surfactant noigen RN10 (polyethylene alkyl phenyl ether) on kaolin wettability and stability was also studied. Clay can also help in stabilizing the suspension by having the effect on its rheological property since viscosity determines the rate of sedimentation according to stokes law. The different types and amount of clay are used to determine the final rheological property of the suspension. Dispersions showing dilant behavior contains 1:1 clay minerals and the pseudoplastic behavior is exhibited by 2:1 clay minerals. The commercialized MAS is a fibrous 2:1 clay containing blends of montmorellonite and seponite [6, 24, 25]. A combination of polyethylene glycol with hectorite improved the suspension stability [26, 27]. The modified hectorite such as quaternary C18 hectorite, Steralkonium hectorite is used in organic media to control viscosity [28].

The use of clay along with polymers has shown beneficial effect on their rheological properties, which has been demonstrated in griseofulvin suspension with MAS and sodium alginate by Dechow et al. [29] in sulfamethoxazole/trimethoprim suspension. The synergistic effect of CMC on properties of MAS such as viscosity,

electrolyte tolerance, smooth flow property has led to the development of Veegum PLUS [30]. A similar synergism has also found in xanthan gum [31, 32].

2.1.2 In emulsion

Clay minerals are also added to pharmaceutical emulsion to prevent coalescence, creaming, phase inversion, breaking, and flocculation. This is due to their ability to wetted by the two liquid phases and be present as a barrier to prevent phase separation. Flocculation can be prevented by clay material due to their zeta potential. The stability of the emulsion is improved with increase in contact angle. They also used in the mechanical production of emulsion by acting as a surface acting agent which can bind in the interfacial layer but do not reduce the interfacial tension and interface. Due to its higher surface area, talc has been used as a emulgent in the cosmetic preparation [18]. The use of bentonite as emulsifying agent is familiar throughout the cosmetic industry. A nail enamel cream contains bentonite as an emulsifier was prepared by Carter [33]. He also proposed specific method of the cream preparation. Vanishing creams and skin protectants also use bentonite in a concentration of 2.5% w/v as emulgent [34]. In order to aid in easy application and adherent effect on the skin surface, clay minerals are added in corn and callus emulsion [34]. They are also added to hand creams as a thickening agent to retain better moisture control. The viscosity of the liquid eye liner formulation is maintained by addition of veegum [34]. Purified bentonite (Polargel NF) has been used as an emulsifying agent in cleansing lotion with HPMC and benzoyl peroxide. This has also been prepared as a cream by the addition of viscosity building agent (Carbomer) [17]. An anti-acne cream emulsion is prepared by using MAS [17]. MAS is also incorporated in cream emulsions for burns, methyl salicylate (analgesic effect), astringent zinc oxide, zirconium oxide and in zinc undecylenate lotions as a emulsifying agent [17]. Certain vitamins enriched skin creams also use MAS as emulsifier [30]. The synergic effect of xanthan gum along with MAS has been seen in zirconium oxide lotion [17]. Wenninger et al. [35] showed the usage of palygorskite as an emulgent (2–5% w/v). The presence of Na^+ and K^+ ions in halite and sylvite and their ability to control micelle size enumerate their use as emulsifying, thickening and anti-caking agent [36]. The long-term stability of pickering emulsions (where dodecane is used as oil phase) is improved by addition of kaolin (15% w/v) without any other additives [37].

2.2 Use of clay as an excipient in solid dosage forms

2.2.1 As diluent

Pharmaceutical oral preparations contain excipients such as diluent, flavorant, binder, disintegrant, pelletizing agent, granulating agent, sweetening agents, film coating agent, lubricant, and desiccants. Each excipient has its own influence on the formulation without interfering with active drug. It enhances the organoleptic and physiochemical property of the formulation. Diluents are selected based on the water solubility and bioavailability of active drug. Formulations with less water soluble drugs are incorporated with water soluble diluents and vice versa. Kaolin exhibit non-hygroscopic nature and low moisture content which determines its effectiveness as a diluent, as high moisture content may affect compressibility, physical and chemical stability of the formulation. Physiochemical parameters of kaolin have a direct impact over compressibility of the formulation [38]. The usage of kaolin as excipient for their adsorbent capacity has to be

properly maintained since high adsorbent capacity can lead to less bioavailability of the drug [38–40]. Diluents are mainly added to the formulation to bulk up the volume and to facilitate easy compression. Diluents account for the 90% in low dose formulation. Product such as slim-well and quantrim use kaolin as bulking agent whereas mecysteine hydrochloride (Gastro resistant tablet) has heavy grade kaolin. Riclasip and co-amoxyclov DST grunenthal uses kaolin as adjuvant [41]. The use of kaolin with metronidazole (antibiotic and antifungal drug, Riazole) reduces its bioavailability, release characteristic and diffusion of drug inside the body [42]. The absorption of D, L-phenylalanine (analgesic and anti-depressant) onto the slurry of colloidal kaolin was showed by Bonner and Flores [43] through in vitro gross adsorption chromatographic study. Kaolin also affect the bioavailability of drugs like phenytoin (anti-seizure drug), promethazine-HCl (sedative and antiallergic drug), chloroquine (anti-malarial), propranolol (vasodilator), quinidine sulphate (cardiac antiarrhythmic drug), phenothiazines (trifluoperazine, fluphenazine, perphenazine, and thioridazine), guanethidine and hydralazine (antihypertensive drugs), procainamide and verapamil (antiarrhythmic drugs) with antidiarrheal Kaopectate® drug [44–49]. It has been reported that Langmuir isotherm was followed in drug absorption by kaopectate which extent the bioavailability but the rate of drug availability is retarded. The double layered adsorption pattern of mebeverine hydrochloride (antispasmodic drug) with kaolin and added electrolytes again follows Langmuir isotherm was studied by Al Gohary. These types of interactions of kaolin can be prevented by increasing the ionic strength of the drug solution and with the presence of $-NH_2$, $-O-$, and benzene ring, as chelating ligands led to the interaction. The presence of di-aromatic ring in naproxen (anti-inflammatory drug) and siloxane surface of kaolin are responsible for their interaction [50]. On other hand, the absorption of ampicillin and warfarin (anticoagulant) with antidiarrheal kaolin-pectin is shown to be unaffected by kaolin [51, 52], which was again conformed by Khalil et al. [53]. In fact, the use of kaolin as diluent in water soluble cationic riboflavin (vitamin B2) has improved the release rate of drug from hard gelatin capsule than any other diluents used. The rate of drug release is pH dependent [54]. The sustained release formulation of pyridoxine hydrochloride (vitamin B6) was prepared by using kaolin as diluent [55]. Vitamin drugs degrade easily in the presence of high moisture content since kaolin exhibit low moisture content the formulation containing vitamin B1 (thiamine) and Vitamin C (ascorbic acid) is more stable on addition of kaolin than other additives [56, 57].

2.2.2 As binders

Binders help to maintain the physical integrity of the solid dosage form owing to their mechanical strength. They also play a vital role in granulation, tableting, encapsulation by acting as a homogeneous dispersed matrix for adhesion of all material in the formulation. On this context, the mixture of kaolin-Eudragit (8% w/w) has been one of the good binders for tableting process. Eudragit is a poly ester based resin which exhibit hydrophilicity and does not get affected by varying pH and also the presence of kaolin help to obtain a uniform polymeric dispersion by differentiating water insoluble and hydrophilic particle within the system. Irrespective of their physiochemical properties, hydrophilic drugs are also blended with low water soluble drug in the kaolin-Eudragit formulation due to their larger permeability. Based on kaolin concentration they can also be used as film coating agent [58, 59]. Minerals like periclase, calcite, and magnesite are added as binders to increase the stomach pH [60].

2.2.3 As disintegrant

The release of drug from the formulation once it reaches inside the body mainly depends on the nature of the disintegrant used during formulation. Disintegrant facilitate breakdown of solid dosage form into smaller particulates. Poor solubility, poor gel forming capacity, good hydration capacity, good molding, flow property, and should not form complex are the required criteria for disintegrants. Both swelling property and ability to decompose at acidic environment of smectite made its use as a disintegrating agent. The presence of negative charge and ability to produce permanent negative surface charges helps kaolin as a disintegrant [61, 62]. A mixture of kaolin with surfactant and cellulose when added to formulation which already has starch as a disintegrant increased its shelf life over a long period of time [63]. Later, the use of kaolin as a positive effect than starch as a disintegrant has been proved [64].

2.2.4 As pelletizing agent

Kaolin proved its efficiency over bentonite by forming pellets which show faster disintegration while the pellets formed by bentonite was only erodible not disintegrable [65]. Kaolin along with biopolymer increase the drug dissolution rate of hydrochlorothiazide by forming pellets that rapidly disintegrated into the dissolution medium [66]. The primary aim of pelletizing agent is to form microspheres of uniform size which can be compressed into tablets or filled into capsules that rapidly disintegrates inside gastrointestinal drug where each pellet act as sustain formulation [67, 68]. Kaolin as a pelletizing agent in comparison with bentonite, talc, veegum and bentonite produce pellets with maximum yield, desirable size and smooth pellets on addition of SLS (5%) over the others [69]. The beneficial effect of crospovidone (5% w/w) and kaolin (25% w/w) with lactose as pelletizing agent for enhancing roundness and sphericity of pellets was demonstrated by Kristensen et al. [65]. The drug dissolution rate of riboflavin was higher with kaolin than microcrystalline cellulose and lactose [66]. Desirable size range and sphericity can be obtained by incorporating high kaolin content. Aerosil 200 (5%) along with kaolin (45%) has huge positive impact on sphericity of pellets [70]. The granulating agent is added to the formulation to improve flow property, density, appearance and uniform drug content, they also aid in compressibility of oral formulation. Wet and dry granulations are most commonly used method of granule preparation. Wet granulation involves wetting, nucleation, coalescence, breakage, and attrition process whereas dry granulation involves direct compression or slugging [71, 72]. Granules of desirable strength, size, cohesion, and uniformity can be produced by mixture of kaolin and sodium chloride (10% w/w) in wet granulation process. The comparative study of kaolin with polyethylene glycol and polyvinyl alcohol as a binder in calcium chloride showed kaolin PVA mixture gave larger yield and size than PGA kaolin mixture [73].

2.2.5 Aid in solubility, dissolution, and lubrication

Kaolin also helps to convert drugs from their crystalline to amorphous state to improve their solubility, dissolution rate, and bioavailability [74–76]. Kaolin was added to ibuprofen in order to convert it to amorphous salt from its crystalline form to facilitate higher dissolution and bioavailability in comparison with standard. Halite can be used to control osmolarity of the solution due to their high solubility in water [77]. Amorphization is inversely proportional to the kaolin concentration [74]. Clays are also used as desiccants due to their hygroscopic nature. Talc is used as lubricant and

to prevent adhesion of powder to the compression pistons due to their soft and unctuous nature [78]. They are also used as flavorant to mask the taste of the formulation.

2.2.6 As coating agent

The use of film coating additive enhance the organoleptic characters of solid dosage form, helps in maintaining stability and control drug release profile [79, 80]. The decrease in the rate of drug release of diphenhydramine chloride, theophylline, and pseudoephedrine hydrochloride pellets coated with Eudragit on addition of kaolin (3:1 of resin) was studied by Ghebre-Sellassie et al. [58]. Kaolin is also added to the film coating of hypericon and kollicoat IR. Kaolin incorporated on the outer shell of triple pressed dyphylline coated tablets showed control release [81].

2.2.7 Enhancer of organoleptic properties

The organoleptic property of a drug can be modified on addition of excipients like pigments and opacifiers into tablets, capsules, syrups, and topical creams. These are necessary to avoid confusion while administering multiple medications and for easy identification of different dosages and help to protect the drugs from photo-oxidative damage. Clay minerals (calcite, rutile, hematite, and magnesite) possess a wide range of color from red, green, black, yellow, and white. Coloring E171 is most used pigment which is a synthetic analogue of white zincite. Synthetic rutile is used on sunscreen lotion as opacifier.

3. Use of clay as an active ingredient

Clay minerals also has its application as active ingredient in pharmaceutical preparation due to their ability to act as antacids, antianemics, mineral supplements, gastric protectors, laxative, antidiarrhoeaics, antibiotics, antiviral agents, wound dressing agent, detoxifier, antitumor agent, anti-inflammatory, and tropical analgesic.

3.1 Antacid

Acidity is caused by excess secretion of HCl in the stomach due to various conditions. Clay minerals overcome acidity either by neutralizing hydrochloric acid or by decomposition of minerals by absorbing H^+ ion on to their surface. Thus, restoring the stomach pH to 7 from 1.5 to 2.5. An effective antacid must increase the pH by three to four units and decrease the free acidity, which is seen in clay minerals like calcite, magnesite, periclase, brucite, and hydrotalcite. Whereas palygorskite, sepioite, montmorillonite, and saponite neutralize acidity by absorbing H^+ ion onto their surface. Their usage also can lead to certain side effects such as renal silica calculi, constipation in case of over accumulation of Ca^{2+} since they form insoluble hydrate phosphate and Mg^{2+} ion produces laxative effect but these effects can be avoided by using different mineral compositions. This combination has also an advantage of sustaining the drug release for example the co-administration of gibbsite with brusite prolonged its antacid action since brusite is fast acting and gibbsite is slow acting antacid [82].

3.2 Wound dressing agent

Wounds characterized by skin abrasion and vascular damage can lead to microbial invasion, toxicity, and even hemorrhagic shock due to uncontrolled bleeding.

This is countered by our body homeostatic response through coagulation of blood which prevents bleeding. Hemostasis follows sequential steps like: (1) thrombin formation is initiated, (2) activation and platelet aggregation (amplification), and (3) fibrin formation to stabilize the platelet clot (propagation). Hemostatic agents provide a physical mesh-like layer which aid in amplification and propagation steps of hemostasis thus leading to platelet aggregation and coagulation. The negative surface charge of kaolin at blood and plasma pH has a drastic effect on its blood clotting potential. The activation of blood coagulation factor XII to its active is done by kaolin on contact with blood and plasma. The active form of factor XII in turn activates factor XI and pre-kallikrein which helps in preventing bleeding. Therefore, many wound dressing products contain kaolin as topical hemostatic agents (Quickclot combat GauzeXL, Quickclotinterventional™) [83–87].

3.3 Peptic ulcer

Peptic ulcer is characterized by thinning of mucosal layer of the stomach due to the mucolytic activity of stomach enzymes, in order to reduce gastric irritation and provide a barrier for mucosal layer several clay minerals are used for their high sorption capacity and non-toxicity. These clay minerals absorb all the gases, toxins, bacteria and even viruses and reduce gastric secretions. They also act as protectants decreasing the glycoprotein degradation in the stomach. But their non-specific action has led to their minimal usage. Even though smectites prevent the pepsin damaging activity over the mucosal layer, their very less time of action and tendency to get degraded in the acidic medium has been a disadvantage but kaolin can be stable and show very low dissolution even at very less pH. They are taken as tablets, suspensions, or powders orally. They dissolve easily in the acidic medium aiding in their easy elimination and absorption [82, 88–90]. Kaolin due to their higher sorptive capacity delay gastric emptying and intestinal transit by enhancing triacylglycerol hydrolysis and promoting the intestinal uptake of non-esterified fatty acid and glucose [91].

3.4 Anti-diarrheal agent and anti-emetics

Kaolin has been used as an API in formulations for gastrointestinal like ASDA stomach upset tablets, Entroclam, or Boots kaolin [92, 93]. Diarrhea is caused by various factors like allergy, bacterial infection, intoxication, and low efficiency of intestinal sorption. It is characterized by increase in fluidity and frequency of evacuation. Anti-diarrhoeaics agents must have very good absorption capacity of excess water as well as gases in the digestive tracts. Activated clay minerals like kaolinite, palygorskite, sepiolite, and montmorillonite can be used against diarrhea for their high sorption capacity. They also prevent diarrhea by forming insoluble salts through release of Ca^{2+} (calcite) and Al^{3+} (gibbsite) ions [94–97]. Pharmaceutical products such as kaolin/pectin (Kaopectate®) and Kaomix® suspensions, kaolin Antacil®, Sainsbury's Diarrhea relief® and Treda® tablets contain kaolin as active ingredient against diarrhea due to hydrophilicity, surface area, microporosity, water osmotic and retention property as well as its antibacterial and antiviral effect (e.g., Norwalk and rotavirus, salmonella, Shigella and *Escherichia coli* bacteria) [98–101]. Minerals rich in Mg^{2+} or Na^+ ion (mirabilite, epsomite, brucite, periclase, and magnesite) can act as laxative by increasing the osmotic pressure of the intestinal content which induces water level increase in the intestine and finally producing liquid feces. They are given as solutions, granules, and suspensions, and these ions are mostly excreted through fecal matter and a small amount through kidney or bile duct. Halite and sylvite are administered as saline through oral or parental

route for the purpose of electrolyte replenishment (Na^+ and K^+). They are excreted through urine. Minerals rich in Cu^{2+} and Zn^{2+} (chalcocite, goslarite, and zincosite) can irritate gastric mucosa and trigger vomiting so they are used as direct emetic agents. When they reach intestine from stomach, they cause diarrhea. They are given orally as solutions. It can also be used to treat metal poisoning by removing them through vomit.

3.5 In anemia and inflammation

The use of clay minerals extends till its usage in disease like anemia. Anemia is caused due to less production of red blood cells which may be due to less availability of Fe^{2+} . This can be treated with melanterite which is rich in Fe^{2+} ion and readily soluble in water. They are given as oral solution; these ions on reaching blood plasma convert into ferric ion by binding with a transferrin and globulin β . The excess is stored in liver, spleen, and bone marrow. Some are excreted through urine, gall bladder, and bile duct. Orally administered halite, epsomite, brucite, periclase, calcite, hydroxyapatite, magnesite, sylvite, melanterite as tablets provide ions such as Ca^{2+} , Na^+ , Ca^{2+} , Fe^{2+} , K^+ , PO_4^{3-} , and Mg^{2+} which are very much essential to our body [82]. Inflammatory response in our body is triggered to produce white blood cells and their mobility towards the injured site from infection through antigens or other harmful micro-organisms. Swelling, redness, pain, and heat are the main symptoms of inflammatory response. Lopez-Galindo and Viseras [102] presented the use of kaolinite poultices as anti-inflammatory drug, since they can absorb the excess fluid content near the infected tissue, which reduces pain and congestion considerably. They also aid in skin cooling by acting as a heat retention agent. Proper care of temperature must be taken while administering these dosages since it can have an effect over its therapeutic action [103–108].

3.6 Anti-bacterial

Minerals like sulfur, goslarite, borax, zincosite, chalcantite, zincite, and alum are highly corrosive and toxic to pathogens in higher concentration hence they can be used as an antiseptic or disinfectant. They are also used as an astringent (chalcantite), bacteriostatic agent (borax), fungicide, hemostatic agent (alum), and for skin damage. The bactericidal activity of clay extends to many drug-resistant bacteria like *Pseudomonas aeruginosa*, *E. coli*, and *Staphylococcus aureus* due to their physical and chemical properties that help them to envelope bacterial cells and interrupting their nutrient uptake, this is due to their high surface attraction towards the bacterial cell wall. Ions present in clay minerals also play an important role in their bactericidal property. Divalent cations like Cu^{2+} and Fe^{2+} are easily transferred and oxidized inside the bacterial cell to produce intercellular hydroxyl radicals which are lethal to them. The tri- or tetravalent cations show their activity inhibiting the influx or efflux pumps. Many modified clays have been reported to have good bactericidal activity, for example the photocatalytic activity of zinc oxide and Ti make TiO_2 (ZnO)/kaolinite make the effective against *Enterococcus faecalis*, *E. coli*, and *Pseudomonas aeruginosa*. Moreover, *Pseudomonas aeruginosa* is also susceptible to kaolin modified with CTAB and Cu. Oral pathogens like *E. coli*, *Bacillus subtilis*, and *Klebsiella pneumonia* are effectively killed by kaolin/iron-porphyrin hybrid. Nano-composite of silver-kaolinite also demonstrated to have antibacterial property [109]. They use clay as an adsorbate to remove pathogenic viruses and certain phages are under investigation since the twentieth century. First it is thought that viruses by electrostatic interaction are adsorbed onto the clay surface due to their valency associated cations and cation exchange capacity but later studies showed

that amino acid and carboxylic residue present on the outer shell viral protein coat is responsible for the net charge and their adsorption into clay minerals depends on pH, ionic strength, and isoelectric points of the clay and virus. Further studies show that hydrophobic interactions of crystallized kaolin show greater affinity for certain bacteriophages. In vitro studies of kaolin against hepatitis C virus, human enteric pathogenic adenoviruses (hAdVs) and adenovirus (HAdV-5) proved kaolin to be an effective material that could be used against certain viral infections [110]. Many substances like heavy metals, toxins, mycotoxins, and overdosed drug compounds can be removed from the gastrointestinal tract by administering kaolin as a detoxifying agent.

3.7 Miscellaneous

Kaolin is found to influence superoxide radicle generation by immunocompetent carcinoma blood cells of Lewis lung in mice this opens a huge area of application for kaolin usage in restorative cancer treatment. Their antitumor property has made it a potential candidate under investigation [92, 100, 110–112]. Minerals like zincite, talc, rutile, hydrozincite, smithsonite, kaolinite, and smectites are used as a protective agent in skin to prevent against certain external environmental condition and pathogens. They have suitable properties like high sorption, non-cytotoxic, little antiseptic and bactericidal as discussed above. They are used as creams, powders, and ointments (REINOL drygard, DP1, kerodex 51, etc.). They are also incorporated in sunscreen formulation to prevent against harmful UV-A and UV-B. Minerals like rutile and zincite absorb, reflect, and scatter the radiation but they may cause skin damage by photocatalytic action this can be overcome by using kaolin as protectant since it shows higher UV protection capacity due to the high Fe_2O_3 content. Kaolin also used to absorb excess moisture, oily secretion, surface lipids, and superficial toxin from the skin surface to prevent acne, blackheads, bacterial, and fungal infections. Even they are used for insect bites to give relieving effect [109].

3.8 Skin protectant

Sulfur containing minerals are extensively used as keratolytic reducers as they are effective against dermatitis, eczemas, and psoriasis. Sulfur reacts with cysteine in the presence of keratinocyte producing hydrogen sulphide which breaks down keratin. Dandruff is treated with cadmium sulphide shampoo. The less common adverse effect of sulfur applied as topical cream is an added advantage [82]. Isotonic collyrium contains dissolved halite which is used as decongestive eye drops for treating eye dryness, irritation, and other ocular discomforts.

4. Use of clay as a drug delivery system

An effective drug delivery system is essential for achieving proper bioavailability of the drug administered. Recent studies have paved way for many new modified drug delivery system that has led to sustained drug deliver, controlled drug delivery, and site-specific drug delivery (Table 2). Each has its own mode of release and application in the body. The modification can be made only through excipients employed. The proposed excipients must possess good delivery efficiency at the same time have inertness, easy availability, cost effective, and low toxicity. Thus, all these are readily available in clay minerals and their physiochemical properties make them a potential candidate for design of MDDS. Clay minerals either in their

native form or modified in certain way to improve their physiochemical properties to aid their use as a drug carrier for delivering system.

4.1 As release retardant

Kaolin (1:1) and smectite (1:2) are the most common used clay groups in the design of MDDS due to their geometrical structure. The side effects like short half-life and requirement of frequent dosage in diclofenac sodium (NSAID) can overcome by intercalating it with MMT that prolong drug release. The toxicity of topically administered chlorhexidine (antibiotic) can be prevented by using Na-MMT as a drug delivery carrier. The photolytic damage of promethazine (antihistamine) when administered topically is reduced by intercalation of drug with Na-MMT. The in vitro activity and controlled release of paclitaxel (anti-cancer) is increased by intercalation with Na-MMT and coating with chitosan (biopolymer). Gallic acid has various properties like poor solubility, permeability, and faster metabolism which make it difficult for dose administration and drug release. The idea of Gallic acid with MMT was suggested and carried to and characterized the drug release profile which showed promising results. A dermal patch prepared using MMT-Na loaded with silver (antimicrobial agent), lidocaine (mild analgesic), and betaine hydrochloride showed a controlled release of lidocaine. The controlled drug release of metformin with Na-MMT was studied in order to reduce the side effect and dosage of drug. But the study concluded that the drug release was highly pH dependent and needed further analysis. MMT enhanced the antibacterial activity with TiO₂ coated with alginate against both gram positive and negative bacteria. Mesalazine (5-Aminosalicylic acid) must reach colon to show its therapeutic action against Crohn's disease but mesalazine is highly absorbed in the acidic environment of stomach. This can be altered and slow drug dissolution in stomach was achieved using MMT-Na encapsulated into alginate beads. Acidification improves clay surface area and increases pores for sorption. These acidified clays was used as a carrier to deliver ciprofloxacin, the acid treatment retarded the drug release due to the changes in the interlayer charges, this also provided insight on the usage of interlayer charge modifications of the clays can be a useful phenomenon for drug delivery. Silver nanoparticles are also loaded with modified clay and their antibacterial activity is characterized and a comparative study between modified and unmodified clay hybrid for their loading capacity and antibacterial activity against *S. aureus* and *E. coli* was done. The results showed that both the loading capacity and antibacterial activity was higher for acidified clay when compared to its native form. Periodontal extended release of tetracycline was achieved by intercalation of drug with MMT hybrid (Veegum HV) and chitosan as mucoadhesive base, the formulation required only once per week. Optimization of gentamycin loaded with another clay hybrid (Veegum F) was done and its antibacterial activity was evaluated, the formulation a delayed drug release up until 8 days. Theophylline was loaded onto MMT hybrid (Veegum F) to prevent the premature gastric drug absorption and to give a sustained release in intestine. Electrostatic interaction with clay hybrid prevents theophylline absorption at the stomach pH and facilitates slower absorption on the intestinal pH. The in vitro antibacterial activity of ciprofloxacin was determined by the type of interaction it forms with the clay hybrid, a weak interaction ensures easier release of drug into the desired site. Another modification of clay minerals which is used in MDDS is functionalization of the interlayers. One such functionalized clay is pillared clay which have large specific surface area and larger porosity due to the cationic exchange with inorganic compounds (4-(dimethylamino)-1-(4-vinylbenzyl) pyridiniumchloride and 1-methyl-3-(4-vinylbenzyl) imidazolium chloride). Ibuprofen loaded into MMT

hybrid pillarized with Fe^{3+} and Fe^{2+} showed a delay in drug release under various physiological conditions. Doxorubicin (anticancer) was loaded into functionalized kaolin showed good drug loading efficiency and therapeutic action.

4.2 Clay-biopolymer combination

Biopolymers can also influence drug delivery by encapsulation or by surface coating over the formulation and help in controlled drug delivery. Hence, clay hybrids are coated with biopolymers to enhance their action. Clay hybrid and biopolymer (chitosan) showed synergistic effect on loading efficiency and drug release of 5-aminosalicylic acid. The oral bioavailability of oxytetracycline (broad spectrum antibiotic) was improved by loading over chitosan-MMT carrier. The cytotoxicity of chlorohexine to fibroblast was reduced by preparing a film carrier made of MMT-chitosan complex. The prepared topical formulation showed a controlled release of drug and reduction of cytotoxicity was also reported. MMT-chitosan glutamate composites also reduced the cytotoxic effects of silver sulfadiazine (skin burns). The result show that electrostatic interaction of MMT with polymer helps improving the drug absorption and the increase an antibacterial activity of formulation was also noted. Apart from chitosan, other biopolymers have been used to prepare drug carriers. A combination of guar gum-MMT hybrid was used to prepare a controlled release formulation of ibuprofen to reduce their side effects on intestinal tracts. The need of frequent dosage of venlafaxine (anti-depressive drug) was reduced by preparing beads with crosslinking of sodium ALG with drug-MMT in CaCl_2 . Olanzapine (schizophrenia and bipolar disorder) was incorporated into different polymer composition and their drug release at different pH was studied and the results were in comparison with the marked drug and an effective controlled release was obtained by cloisite-drug with a blend of polymers (Alginate and xanthan gum). The solubility of curcumin (anticancer, anti-inflammatory and antibacterial agent) can be increased by dispersing the drug with CMC and loading into MMT, the role of MMT here is to improve the drug release in the acidic environment. A transdermal DDS was prepared from MMT nanocomposite, pectin, and methyl cellulose which is used to load ketorolac (NSAID). The formulations showed immediate release of drug from the nanocomposite layer but the increase in MMT showed controlled drug release. The PLA microspheres of 6-mercaptopurine (anticancer drug) with MMT showed a faster release rate and increased the drug solubility. The presence MMT also helps to control the drug release. The performance of a pH dependent swelling polymer (poly acrylamide-co-maleic acid) was improved by the addition of MMT hybrid, it exerted a control over the caffeine drug release even during sudden pH transitions. A prolonged oral DDS was prepared for 1,3,4-oxa(thia)diazole (antifungal, antibiotic, analgesic and anti-inflammatory agent) by preparing nanocomposite using MMT hybrid. A site specific DDS was developed using MMT-polymer hybrid for anticancer treatment by co administration of doxorubicin and methotrexate with ciprofloxacin (antibiotic). Specificity of the DDS depends on the pH of the tumor cells. The results showed that the entire three drugs exhibit delayed drug release, where the anticancer drugs showed similar release profile and ciprofloxacin showed a different release profile at pH 5.8 and 4. PLGA is another biopolymer which is extensively used as carrier for drug administration. A double emulsion of atenolol with PLGA and MMT was prepared by Lal and Datta to increase the half-life and dissolution rate of the drug. The result suggested a controlled drug release in both acidic as well as basic medium with marking changes in the acidic medium. The hydrophobic drug (dexamethasone) was also intercalated with PLGA and MMT by Jain and Datta to lower the risk of side effects and achieve effective plasma concentration at minimal dosage. PLGS-MMT

nanocomposite is used as a carrier for insulin. In vitro studies by Lal et al. suggested the protective nature of MMT even in acidic conditions and also they do not affect the HEK-293 cells growth. A triblock (PCLA-PEG-PCLA) copolymer hydrogel of MMT-gemcitabine (anticancer) was prepared for the intravenous administration of drug since the drug is metabolized rapidly and require high dose. In vitro drug release studies suggested that MMT significantly reduced the drug release and the side effects. Nanocomposite of MMT hybrid with HEMA was used to modify the dissolution profile of paracetamol by Bounabi et al. The inclusion of MMT improved the drug encapsulation of paracetamol in the PLA-drug nanocomposite. A site specific DDS was prepared for doxorubicin was prepared using MMT hybrid with PE-5000/PEG750 polymer. Organoclay (MMT-PVP hybrid) nanocomposite was used to encapsulate copaiba oleoresin a natural derivative used against endometriosis. The nanocomposite showed effective controlled drug release at acidic pH. A polymeric composite (PVA, CS and MMT) was prepared to encapsulate 5-fluorouracil (anticancer) in order to compensate its poor oral absorption and rapid metabolism. The results also indicate that the drug loading efficiency and drug release depends on the MMT concentration. Clay minerals like halosite and fibrous phyllosilicates have MDDS application due to their tubular and ribbon shaped structure. For example, the Hal nanotubes can adapt to any morphology making them used for wide variety of applications in MDDS. Various antibiotic like ciprofloxacin, chlorpheniramine, tetracycline, diphenhydramine has been loaded on to the hal nanotubes and investigated. Cationic exchange capacity and pH determines the drug loading capacity on to the hal nanotubes. Thermodynamic equilibrium also affect the drug loading in hal nanotubes as in the case of isoniazid (antituberculosis drug). The immobilization of binase (RNase enzyme) which is used in the genetic treatment of cancer was done and an enhanced anticancer property was reported. Vancomycin and breviscapine has been loaded on to hal nanotubes by vacuum cycle and the resultant complex showed a sustained release of drugs. Amoxicillin loaded onto Hal nanotubes are combined with biopolymers (PLGA and Chitosan) and the drug release was studied the results suggest a sustained release is obtained on both formulations with and without biopolymers than biopolymer-drug complex. PMMA was coated onto paclitaxel-hal nanotube complex to improve the anticancer activity of the drug. Volatile drugs are also adsorbed onto the clay minerals which help in preventing the evaporation of those drugs and retaining their therapeutic action. The volatile drug absorption of MMT, hal nanotubes and palygorskite was evaluated by loading carvacrol (treat skin lesions). Good adsorption was seen in palygorskite. Veegum HS and sepiolite improved the solubility and dissolution rate of praziquantel (treatment of schistosomiasis) in both acidic and basic environment. Higher dissolution was achieved by oxaprozin (Non-steroidal anti-inflammatory agent) on mixing it with clay hybrid of palygorskite and sepiolite modified with cyclodextrin. Curcumin was loaded with both functionalized clay and cellulose-MMT complex to improve its site specific action and synergic effect on wound healing. A phospholipid nanocomposite of hal nanotubes was prepared to achieve a sustained release of doxorubicin. The electrostatic interaction and intermolecular hydrogen bonding between palygorskite and chitosan was studied for its usage as a drug carrier for 5-aminosalicylic acid. Sepiolite is also used with chitosan as drug carrier for tetracycline and cefazolin. In vitro studies show the swelling of gel is facilitated by chitosan whereas the drug release is controlled by crosslinking of polyvinylacrylate (PVA). The synergistic effect of hydroxypropylmethylcellulose acetate succinate along with atorvastatin and celecoxib for colon cancer is due to their effective solubility in basic pH. The controlled release of drug in colon is achieved by the preparing microspheres of hal nanotubes and HPMCAS loaded with anticancer drugs.

5. Pharmaceutical clay in share market

The clay minerals are exported worldwide for their various applications in construction and pharmaceutical preparations. Based of the application the clay mineral export is classified as tableware, sanitary ware, medicinal applications. The key minerals are bentonite and kaolin which accounts for major export. Bentonite is exported as sodium, calcium and sulfur bentonite. The global market demand of bentonite (**Figure 2a and b**) was 22.68 million metric ton by 2016 and estimated to be 25.15 Million metric ton by 2021 with a CAGR increase of 2.12%. The global market share of bentonite by 2017 was 1.43 billion and estimated to be increasing scale due to the market demand and increase in the applications of clay minerals. The major region of export is classified as Asia Pacific, North America, Europe and Rest of the world with Asia and North America accounting for most. The major companies exporting clay minerals are Ashapura groups (India’s major exporter), Imerys(sandB), Taiko group, Huawei Bentonite, Theile kaolin company, Kaolin A.D, J.M.Huber, Daleco resources.

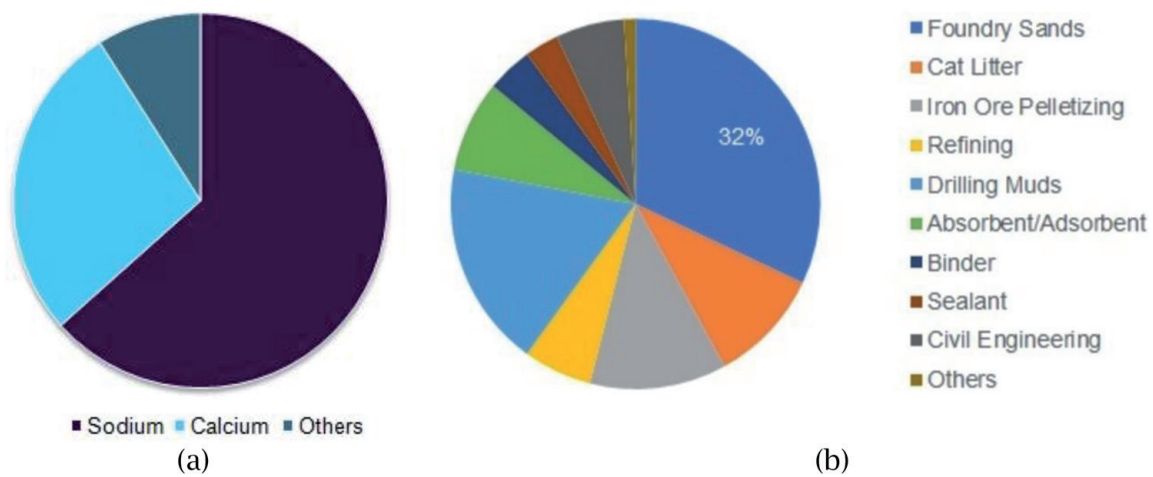


Figure 2.
(a) Bentonite classification based on minerals. (b) Bentonite usage on global demand scale.

6. Conclusion and outlook

From the moment of discovery clay minerals have been immensely useful to human life in both ceramic and health. Their usage in health care has made it a essential compound in many pharmaceutical preparations. Their inertness, low toxicity, versatile physiochemical properties and cost effectiveness has increased its usage in pharma industries. At the same time precautions must be taken while incorporating higher doses of clay and while co-administering clay with drug. Since some clay has been reported to reduce the efficacy and bioavailability of certain classes of drugs like antacid and in higher doses it might cause tissue toxicity. The understanding of surface chemistry and particle size distribution of clay minerals has led the pharmaceutical field in many directions and future perspectives. Their unique structure which helps them to absorb material onto their layered sheets has opened a wide variety of applications in drug delivery. Their ability to control and alter drug release profile can been exploited in many ways to design a effective drug delivery system. Further advancements in nanotechnology have helped to synthesize and modify this clay mineral to enhance their physiochemical properties and their usage as excipient. Though clay and their minerals are used in its natural

state for drug delivery, some require additional modification for their usage and this modification plays a key role in determining the economical aspect of drug designing. The development of machinery which helps us to understand better about various unknown properties of clay minerals which were not understood before will aid us to utilize clay minerals in various other applications.

Author details

Nandakumar Selvasudha^{1*}, Unnikrishnan-Meenakshi Dhanalekshmi^{2*},
Sekar Krishnaraj³, Yogeewarakannan Harish Sundar³, Nagarajan Sri Durga Devi³
and Irisappan Sarathchandiran¹


¹ School of Pharmacy, Sri Balaji Vidyapeeth Deemed to be University, Puducherry, India

² Oman Medical College, Bowshar Campus, Muscat, Sultanate of Oman

³ Department of Biotechnology, Anna University, Chennai, India

*Address all correspondence to: nkselvasudha@gmail.com
and dhanamnair2013@gmail.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Novelli G. Applicazioni medicale e igieniche delle bentoniti. In: Veniale F, editor. Atti Convegno "Argille Curative", Salice Terme/PV. Gruppo Italy. AIPEA; 1996. pp. 25-43
- [2] Robertson RHS. Cadavers, cholera and clays. Mineralogical Society of Great Britain & Ireland. 1996;113:3-7
- [3] Carretero MI. Clay minerals and their beneficial effects upon human health. A review. Applied Clay Science. 2002;21:155-163
- [4] Veniale F, Barberis E, Carcangiu G, Morandi N, Setti M, Tamanini M, et al. Formulation of muds for pelotherapy: Effects of "maturation" by different mineral waters. Applied Clay Science. 2004;25:135-148
- [5] Viseras C, Lopez-Galindo A. Pharmaceutical applications of some Spanish clays _sepiolite, palygorskite, bentonite: Some preformulation studies. Applied Clay Science. 1999;14:69-82
- [6] Viseras C, Aguzzi C, Cerezo P, Lopez-Galindo A. Uses of clay minerals in semisolid health care and therapeutic products. Applied Clay Science. 2007;36:37-50
- [7] Gomes CSF, Pereira Silva JB. Minerals and Human Health. Benefits and Risks. Centro de Investigação "Minerais Industriais e Argilas". Fundação para a Ciência e a Tecnologia do Ministério da Ciência, Tecnologia e Ensino Superior. Aveiro (Portugal); 2006
- [8] Carretero MI, Gomes C, Tateo F. Clays and human health. In: Bergaya F, Theng BKG, Lagaly G, editors. Handbook of Clay Science. Amsterdam: Elsevier; 2006. pp. 717-741
- [9] Porubcan LS, Born GS, White JL, Hem SL. Interaction of digoxin and montmorillonite: Mechanism of adsorption and degradation. Journal of Pharmaceutical Sciences. 1979;68:358-361
- [10] Forteza M, Galan E, Cornejo J. Interaction of dexamethasone and montmorillonite. Adsorption – degradation process. Applied Clay Science. 1989;4:437-448
- [11] Cornejo J, Hermosin MC, White JL, Barnes JR, Hem SL. Role of ferric iron in the oxidation of hydrocortisone by sepiolite and palygorskite. Clays and Clay Minerals. 1983;31:109-112
- [12] Forteza M, Cornejo J, Galan E. Effects of fibrous clay minerals on dexamethasone stability. In: Konta J, editor. Proceedings of the Tenth Conference on Clay Minerals and Petrol, Ostrava. Prague: Universitas Carolina; 1988. pp. 281-286
- [13] McGinity JW, Lach JL. Sustained-release applications of montmorillonite interaction with amphetamine sulfate. Journal of Pharmaceutical Sciences. 1977;66:63-66
- [14] Porubcan LS, Serna CJ, White JL, Hem SL. Mechanism of adsorption of clyndamicin and tetracycline by montmorillonite. Journal of Pharmaceutical Sciences. 1978;67:1081-1087
- [15] Iwuagwu MA, Aloko KS. Adsorption of paracetamol and chloroquine phosphate by some antacids. The Journal of Pharmacy and Pharmacology. 1992;44:655-658
- [16] Del Hoyo C, Vicente MA, Rives V. Application of phenyl salicylate–sepiolite systems as ultraviolet radiation filters. Clay Minerals. 1998;33:467-474
- [17] Sarfaraz N, editor. Handbook of Pharmaceutical Manufacturing Formulations. Cambridge: CRC Press; 2004

- [18] Gabriel DM. Vanishing and foundation creams. In: Harry RG, editor. *Harry's Cosmeticology. The Principles and Practice of Modern Cosmetics*. Vol. I. 6th ed. London: Leonard Hill Books; 1973. p. 83
- [19] Mathews BA, Rhodes CT. Use of the Derjaguin, Landau, Verwey and Overbeek theory to interpret pharmaceutical suspension stability. *Journal of Pharmaceutical Sciences*. 1970;**59**:521-525
- [20] Russel WB, Saville DA, Schowalter WR. *Colloidal Dispersions*. Cambridge: Cambridge University Press; 1995. p. 525
- [21] Vanderbilt Report. Technical Information: "VEEGUM-The Versatile Ingredient for Pharmaceutical Formulations". R.T. Vanderbilt Company Bulletin No. 91R. 1984. Available from: www.rtvanderbilt.com
- [22] Schott H. Controlled flocculation of coarse suspensions by colloidal dispersed solids I: Interaction of bismuth subnitrate with bentonite. *Journal of Pharmaceutical Sciences*. 1976;**65**:855-861
- [23] Sweetman SC. *Martindale: The Complete Drug Reference*. 34th ed. London: Pharmaceutical Press; 2005. p. 2756
- [24] Viseras C, Meeten GH, López GA. Pharmaceutical grade phyllosilicate dispersions: The influence of shear history on floc structure. *International Journal of Pharmaceutics*. 1999;**182**:7-20
- [25] Viseras C, Cerezo P, Meeten GH, López-Galindo A. One dimensional filtration of pharmaceutical grade phyllosilicate dispersions. *International Journal of Pharmaceutics*. 2001;**217**:201-213
- [26] Omar SM, El-Nahhas SA, Khalil RM, Salama HA. Effect of polyethylene glycols on the rheological characteristics of Macaloid dispersions. *Journal of Drug Research*. 1994;**21**(1-2):91-103
- [27] Ash M, Ash I. *Handbook of Pharmaceutical Additives*. 2nd ed. Endicott: Synapse Information Resources; 2002. p. 487
- [28] Clarke MT. Rheological additives. In: Laba D, editor. *Rheological Properties of Cosmetics and Toiletries*. New York: Marcel Dekker; 1994. pp. 55-152
- [29] Dechow HJ, Von Dölcher D, Hübner G, Kim S, Lämmerhirt K, Pich CH, et al. Zurentwicklung von oralesdareichungsformen der kombinationsulfamoxol/trimethoprim (CN3123). *Arzneimittel-Forschung*. 1976;**26**:596-613
- [30] Vanderbilt. Technical Information. 2006. Available from: www.rtvanderbilt.com
- [31] Kovacs P. Useful incompatibility of xanthan gum with galactomannans. *Food Technology*. 1973;**27**(3):26-30
- [32] Ciullo PA. Rheological properties of magnesium aluminum silicate/xanthan gum dispersions. *Cosmetic Chemist*. 1981;**32**:275-285
- [33] Carter HM. Fingernail Cleaning Composition. US patent 2197630; 1940
- [34] Alexander P. *Harry's Cosmeticology. The Principles and Practice of Modern Cosmetics*. Vol. I. 6th ed. London: Leonard Hill Books; 1973
- [35] Wenninger JA, Canterbury RC, McEwen GN Jr, editors. *International Cosmetic Ingredient Dictionary and Handbook*. Vol. 1-3. 8th ed. Washington, DC: Cosmetic, Toiletry, and Fragrance Association; 2000
- [36] McDonald C, Richardson C. The effect of added salts on solubilization

by a nonionic surfactant. *The Journal of Pharmacy and Pharmacology*. 1981;**33**:38-39

[37] Kpogbemabou D, Lecomte-Nana G, Aimable A, Bienia M, Niknam V, Carrion C. Oil-in-water Pickering emulsions stabilized by phyllosilicates at high solid content. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*. 2014;**463**:85-92

[38] Shalini S. Advantages and applications of nature excipients: A review. *Asian Journal of Pharmaceutical Sciences*. 2012;**2**(1):30-39

[39] Niazi SK. *Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products*. Cambridge: CRC Press; 2004

[40] King RE, Schwartz JB. Oral solid dosage forms. *Remington's Pharmaceutical Sciences*. 1985;**17**:1603-1632

[41] NICE. Drug reports (THR 15670/0020), (PL 14894/0297), (PL: 21727/0018-23). 2017. Available from: <http://www.evidence.nhs.uk/> [Accessed: 12 September 2017]

[42] Aleanizy FS, Alqahtani F, Al Gohary O, El Tahir E, Al SR. Determination and characterization of metronidazole-kaolin interaction. *Society of Professional Journalists*. 2015;**23**:167-176

[43] Bonner WA, Flores J. On the asymmetric adsorption of phenylalanine enantiomers by kaolin. *Currents in Modern Biology*. 1973;**5**:103-113

[44] McElnay JC, D'Arcy PF, Throne O. Effect of antacid constituents, kaolin and calcium citrate on phenytoin absorption. *International Journal of Pharmaceutics*. 1980;**7**:83-88

[45] McElnay JC, Sidahmed AM, D'Arcy PF. Experimental modeling of drug absorption and drug absorption interactions. *International Journal of Pharmaceutics*. 1986;**31**:107-117

[46] Naggar VFB, Boraie NA, Shams-Eldeen MA. In vitro availability of promethazine-HCl in the presence of some commercial antacids. *International Journal of Pharmaceutics*. 1986;**28**:239-247

[47] Moustafa MA, Al-Shora HI, Gaber M, Gouda MW. Decreased bioavailability of quinidine sulphate due to interactions with adsorbent antacids and antidiarrheal mixtures. *International Journal of Pharmaceutics*. 1987;**34**:207-211

[48] Moustafa MA, Babhair SA, Kouta HI. Decreased bioavailability of some antipsychotic phenothiazines due to interactions with adsorbent antacid and antidiarrheal mixtures. *International Journal of Pharmaceutics*. 1987;**36**:185-189

[49] Moustafa MA, Gouda MW, Tariq M. Decreased bioavailability of propranolol due to interactions with adsorbent antacids and antidiarrheal mixtures. *International Journal of Pharmaceutics*. 1986;**30**:225-228

[50] Yu C, Bi E. Roles of functional groups of naproxen in its sorption to kaolinite. *Chemosphere*. 2015;**138**:335-339

[51] Gouda MW. Effect of an antidiarrheal mixture on the bioavailability of tetracycline and ampicillin. *Abstracts of 21st Meeting of Academy of Pharmaceutical Sciences*. 1976;**6**:117

[52] Albert KS, DeSante KA, Welch RD, DiSanto AR. Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycine.

Journal of Pharmaceutical Sciences.
 1978b;**67**:1579-1582

[53] Khalil SAH, Mortada LM, El-Khawas M. Decreased bioavailability of ampicillin and amoxycillin in presence of kaolin. *International Journal of Pharmaceutics*. 1984;**19**:233-238

[54] Khalil SAH, Mortada LM, Shams-Eldeen MA, El-Khawas MM. The In-vitro uptake of a low dose drug (riboflavin) by some adsorbents. *Drug Development and Industrial Pharmacy*. 1987;**13**(3):547-563

[55] Onyishi VI, Chime SA, Adibe CV. Formulation of pyridoxine hydrochloride sustained release capsules: Effect of propylene glycol co-solvent on the in vitro release. *African Journal of Pharmacy and Pharmacology*. 2013;**7**(15):809-815

[56] Wai KN, DeKay HG, Banker GS. Stability of vitamins A, B1, and C in selected vehicle matrices. *Journal of Pharmaceutical Sciences*. 1962;**51**(11):1076-1080

[57] Nokhodchi A. An overview of the effect of moisture on compaction and compression. *Pharmaceutical Technology*. 2005;**2**:46-66

[58] Ghebre-Sellassie I, Gordon RH, Middleton DL, Nesbitt RU, Fawzi MB. A unique application and characterization of Eudragit® E30D film coatings in sustained release formulations. *International Journal of Pharmaceutics*. 1986;**31**:43-54

[59] Nesbitt RU. Effect of formulation components on drug release from multiparticulates. *Drug Development and Industrial Pharmacy*. 1994;**20**:3207-3236

[60] Patel H, Stalcup A, Dansereau R, Sakr A. The effect of excipients on the stability of levodopa sodium

pentahydrate tablets. *International Journal of Pharmaceutics*. 2003;**264**:35-43

[61] Mohanachandran PS, Sindhumol PG, Kiran TS. Superdisintegrants an overview. *International Journal of Pharmaceutical Sciences Review and Research*. 2011;**6**(1):105-109

[62] Gopinath H, Venugopal KS, Shanmugasundaram S, Bada PK. A brief review on disintegrants. *Journal of Chemical and Pharmaceutical Sciences*. 2012;**5**(3):105-112

[63] Ward JB, Trachtenberg A. Evaluation of tablet disintegrants. *Drug and Cosmetic Industry*. 1962;**91**:35-36

[64] Lowenthal W. Disintegration of tablets. *Journal of Pharmaceutical Sciences*. 1972;**61**(11):1695-1711

[65] Kristensen J, Schæfer T, Kleinebudde P. Development of fast-disintegrating pellets in a rotary processor. *Drug Development and Industrial Pharmacy*. 2002;**28**(10):1201-1212

[66] Goyanes A, Souto C, Martínez-Pacheco R. Chitosan-kaolin coprecipitate as disintegrant in microcrystalline cellulose-based pellets elaborated by extrusions pherionization. *Pharmaceutical Development and Technology*. 2013;**18**(1):137-145

[67] Manivannan R, Parthiban KG, Sandeep G, Balasubramaniam A, Senthilkumar N. Multiparticulate drug delivery systems: Pellet & pelletization technique. *Drug Discovery Today*. 2010;**2**(5):233-237

[68] Srivastava S, Mishra G. Fluid bed technology: Overview and parameters for process selection. *International Journal of Pharmaceutical Sciences and Drug Research*. 2010;**2**(4):236-246

- [69] Law MFL, Deasy PB. Effect of common classes of excipients on extrusion spheronization. *Journal of Microencapsulation*. 1997;**14**(5):647-657
- [70] Deasy PB, Gouldson MP. In vitro evaluation of pellets containing enteric coprecipitates of nifedipine formed by non-aqueous spheronization. *International Journal of Pharmaceutics*. 1996;**132**:131-141
- [71] Agrawal R, Naveen Y. Pharmaceutical processing – A review on wet granulation technology. *International Journal of Pharmaceutical Frontier Research*. 2011;**1**(1):65-83
- [72] Shanmugam S. Granulation techniques and technologies: Recent progresses. *BioImpacts: BI*. 2015;**5**(1):55-63
- [73] Chow AHL, Leung MWM. A study of the mechanisms of wet spherical agglomeration of pharmaceutical powders. *Drug Development and Industrial Pharmacy*. 1996;**22**(4):357-371
- [74] Mallick S, Pattnaik S, Swain K. Current perspectives of solubilization: Potential for improved bioavailability. *Drug Development and Industrial Pharmacy*. 2007;**33**:865-873
- [75] Panchagnula R, Bhardwaj V. Effect of amorphous content on dissolution characteristics of rifampicin. *Drug Development and Industrial Pharmacy*. 2008;**34**:642-649
- [76] Qi S, McAuley WJ, Yang Z, Tipduangta P. Physical stabilization of low-molecular weight amorphous drugs in the solid state: A material science approach. *Therapeutic Delivery*. 2014;**5**(7):817-841
- [77] Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical industry. Part I. Excipients and medical applications. *Applied Clay Science*. 2009;**46**:73-80
- [78] Wedderburn DL. Baby preparations. In: Harry RG, editor. *Harry's Cosmeticology. The Principles and Practice of Modern Cosmetics*. Vol. I. 6th ed. London: Leonard Hill Books. 1973:543
- [79] Felton LA, McGinity JW. Influence of insoluble excipients on film coating systems. *Drug Development and Industrial Pharmacy*. 2002;**28**(3):225-243
- [80] Felton LA, Porter SC. An update on pharmaceutical film coating for drug delivery. *Expert Opinion on Drug Delivery*. 2013;**10**(4):421-435
- [81] Zoglio MA, Maulding HV, Carstensen JT. Linearization of drug delivery from sustained-release dosage forms, synthetic gel systems. *Drug Development and Industrial Pharmacy*. 1996;**22**(5):431-437
- [82] Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical and cosmetic industries. Part II. Active ingredients. *Applied Clay Science*. 2010;**47**:171-181
- [83] Hermans MH. Wounds and ulcers: Back to the old nomenclature. *Wounds*. 2010;**22**(11):289-293
- [84] Glick JB, Kaur RR, Siegel D. Achieving hemostasis in dermatology – Part II: Topical hemostatic agents. *Indian Dermatology Online Journal*. 2013;**4**(3):172-176
- [85] Smith AH, Laird C, Porter K, Bloch M. Haemostatic dressings in prehospital care. *Emergency Medicine Journal*. 2013;**30**:784-789
- [86] Pourshahrestani S, Zeimaran E, Djordjevic I, Kadri NA, Towler MR. Inorganic hemostats: The state-of-the-art and recent advances. *Materials*

Science and Engineering: C.
 2016;**58**:1255-1268

[87] Z-Medica. Informative Website of QuikClot® Hemostatic Devices. 2017. Available from: <http://www.quikclot.com/> [Accessed: 12 September 2017]

[88] Droy-Lefaix MT, Tateo F. Clays and clay minerals as drugs. In: Bergaya F, Theng BKG, Lagaly G, editors. *Handbook of Clay Science*. Amsterdam: Elsevier; 2006. pp. 743-752

[89] Leonard AJ, Droy-Lefaix MT, Allen A. Pepsin hydrolysis of the adherent mucus barrier and subsequent gastric mucosal damage in the rat: Effect of diosmectite and 16, 16 dimethyl prostaglandin E2. *Gastroentérologie Clinique et Biologique*. 1994;**8**:609-616

[90] Rozalen M, Huertas FJ, Brady PV. Experimental study of the effect of pH and temperature on the kinetics of montmorillonite dissolution. *Geochimica et Cosmochimica Acta*. 2009;**73**:3752-3766

[91] Habold C, Reichardt F, Le Maho Y, Angel F, Liewig N, Lignot J, et al. Clay ingestion enhances intestinal triacylglycerol hydrolysis and non-esterified fatty acid absorption. *British Journal of Nutrition*. 1985;**102**:249-257

[92] Kikouama OJR, Balde L. From edible clay to a clay-containing formulation for optimization of oral delivery of some trace elements: A review. *International Journal of Food Sciences and Nutrition*. 2010;**61**(8):803-822

[93] Constancio J, Pereira-Derderian DTB, Menani JV, De Luca Jr LA. Mineral intake independent from gastric irritation or pica by cell-dehydrated rats. *Physiology & Behavior*. 2011;**104**:659-665

[94] Jones BF, Galán E. Sepiolite and palygorskite. In: Bailey SW, editor. *Hydrous Phyllosilicates*. Reviews in

Mineralogy. Vol. 19. Washington, DC: Mineralogical Society of America; 1988. pp. 631-674

[95] Christidis GE, Scott PW, Dunham AC. Acid activation and bleaching capacity of bentonites from the islands of Milos and Chios, Aegean, Greece. *Applied Clay Science*. 1997;**12**:329-347

[96] Vicente Rodríguez MA, López González JD, Bañares Muñoz MA. Acid activation of a Spanish sepiolite: Physicochemical characterization, free silica content and surface area of products obtained. *Clay Minerals*. 1994;**29**:361-367

[97] Aparicio P, Galán E. Mineralogical interference on kaolinite crystallinity index measurement. *Clays and Clay Minerals*. 1999;**47**:12-27

[98] Clark A, Ede R. Acute Diarrhoea: Causes and Recommended Management. 2011. Available from: www.prescriber.co.uk [Accessed: 12 September 2017]

[99] Primandini P, Hasanah AN, Adi WA, Budianto E, Sudirman S. The effect of calcination temperature on toxin adsorption materials for diarrheal diseases. *Indonesian Journal of Materials Science*. 2012;**13**(3):230-235

[100] Wardhana YW, Hasanah AN, Primandini P. Deformation and adsorption capacity of kaolin that is influenced by temperature variation on calcination. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2014;**6**(3):1-2

[101] Pieszka M, Luszczynski J, Hedrzak M, Goncharova K, Pierzynowski SG. The efficacy of kaolin clay in reducing the duration and severity of heat' diarrhea in foals. *Turkish Journal of Veterinary and Animal Sciences*. 2016;**40**(3):323-328

- [102] López-Galindo A, Viseras C. Pharmaceutical and cosmetic applications of clays. In: Wypych F, Satyanarayana KG, editors. *Clay Surfaces: Fundamentals and Applications*. Amsterdam: Elsevier Academic Press; 2004. pp. 267-289
- [103] Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;**454**:428-435
- [104] Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *Journal of Applied Physiology*. 2010;**109**:1221-1228
- [105] Cornejo-Garrido H, Nieto-Camacho A, Gómez-Vidales V, Ramírez-Apan MT, Angel P, Montoya JA, et al. The anti-inflammatory properties of halloysite. *Applied Clay Science*. 2012;**57**:10-16
- [106] Caglar B. Structural characterization of kaolinite-nicotinamide intercalation composite. *Journal of Molecular Structure*. 2012;**1020**:48-55
- [107] Cervini-Silva J, Camacho AN, Kaufhold S, Ufer K, Jesús ER. The anti-inflammatory activity of bentonites. *Applied Clay Science*. 2015;**118**:56-60
- [108] Cervini-Silva J, Camacho AN, Palacios E, Angel P, Pentrak M, Pentrakova L, et al. Anti-inflammatory, antibacterial, and cytotoxic activity by natural matrices of nano-iron(hydr) oxide/halloysite. *Applied Clay Science*. 2016;**120**:101-110
- [109] Awad ME, López-Galindo A, Setti M, El-Rahmany MM, Iborra CV. Kaolinite in pharmaceuticals and biomedicine. *International Journal of Pharmaceutics*. 2017;**533**:34-48
- [110] Tiwary AK, Poppenga RH, Puschner B. In vitro study of the effectiveness of three commercial adsorbents for binding oleander toxins. *Clinical Toxicology*. 2009;**47**:213-218
- [111] Carraro A, De Giacomo A, Giannossi ML, Medici L, Muscarella M, Palazzo L, et al. Clay minerals as adsorbents of aflatoxin M1 from contaminated milk and effects on milk quality. *Applied Clay Science*. 2014;**88-89**:92-99
- [112] Misyak SA, Burlaka AP, Golotiuk VV, Lukin SM, Kornienko PL. Antiradical, antimetastatic and antitumor activity of kaolin preparation Kremnevit. *Galician Medical Journal*. 2016;**23**(1):44-47