Review Article

Nanoclay Drug Delivery System

R. Suresh1*, S.N. Borkar1, V.A. Sawant1, V.S. Shende1, S.K. Dimble2
1Sharadchandra Pawar College of Pharmacy, Pune, India.
2Vital Health Care Pvt, Ltd, Satpur M.I.D.C., Nashik, India.

ABSTRACT: The concept is based on the recognition that nanometer sized inert inorganic particles, such as nanometer sized clay particles, can be incorporated into a polymeric host carrier, in order to control the diffusion rate of a dispersed slow-release material. A nano-clay particle reduces the porosity of the polymer, or otherwise obstructs the diffusion of the active material being released, thereby increasing the length of the path of the diffusion through the host polymer. This further slows the rate of release of the slow-release material. Clay minerals are widely used materials in drug products both as excipients and active agents. Drug–clay interactions have been observed as a possible mechanism to modify drug release and/or target drug release or even improve drug dissolution. Finally, new strategies are reported for increasing drug stability and simultaneously modifying drug delivery patterns through the use of clay minerals.

KEYWORDS: Clays; Modified drug release; Cation-exchange; Montmorillonite

Introduction

Clays are inexpensive materials, which can be modified by ion exchange, metal/ metal complex impregnation; pillaring and acid treatment to develop catalysts with desired functionality. Nanoclay can be obtained by simply the ion exchange reaction of hydrophilic clay with an organic cation such as an alkyl ammonium or phosphonium ion. The inorganic ions, relatively small (sodium), are exchanged with more voluminous organic onium cations. This ion-exchange reaction has two consequences; first, the gap between the single sheets is widened, enabling organic cations chain to move in between them and second, the surface properties of each single sheet are changed from being hydrophilic to hydrophobic or organophilic (Giannelis et al., 1996).

Nanoclays are minerals which have a high aspect ratio and with at least one dimension of the particle in the nanometer range. The most important factor is the aspect ratio of the clay particle. The clays having a platy structure and a thickness of less than one nanometer are the clays of choice. The length and width of the choice clays are in the micron range. Aspect ratios of the choice clays are in the 300:1 to 1,500:1 range. The surface area of the exfoliated platelets is usually in the range of 700 meters squared per gram. The nano clays that researchers have concentrated on are listed below;

1. Hydrotalcite
2. Montmorillonite
3. Mica Fluoride
4. Octasilicate

Hydrotalcite and Octasilicate have limits of use both from a physical and cost standpoint. The mica fluoride is synthetic clay while the monmorillonite is a natural one. The montmorillonite clays have had the widest acceptability for use in polymers (Forni et al., 1989).

Montmorillonite Nano Clays

Montmorillonite nano clays are unique clays having a platy structure with a unit thickness of one nanometer or less. This clay also has an aspect ratio in the 1000:1 range. Because montmorillonite clay is hydrophilic, it is not compatible with most polymers and must be chemically modified to make its surface more hydrophobic. The most widely used surface treatments are ammonium cations, which can be exchanged for existing cations already on the surface of the clay.

Nanoclay overview (Gordon et al., 2007).

Mechanisms of clay –drug interactions

Clay minerals are naturally occurring inorganic cationic exchangers and so they may undergo ion exchange with basic drugs in solution. Smectites, especially montmorillonite and saponite, have been the more commonly studied because of their higher cation exchange capacity compared to other pharmaceutical silicates (such as talc, kaolin and fibrous clay minerals)

Nevertheless; there are several mechanisms that may be involved in the interaction between clay minerals and organic molecules (Patel et al., 1999, Garces et al., 2000).
Fig. 1 The structure of 2:1 layered silicates treatment.

Fig. 2 Idealization of clay–drug complexation and in vivo drug release mechanisms. (clay mineral surface charge (−); compensating cations (a+); cationic drug (X+); drug associated anions (Y−); in vivo counter ions (A+); anions associated with the counter ions (B−)).

Table 1 Interactions between clay minerals and organic compounds.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mineral examples</th>
<th>Organic functional groups involved</th>
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</thead>
<tbody>
<tr>
<td>Hydrophobic interaction</td>
<td>Any clay with neutral sites (e.g., kaolinite, smectites)</td>
<td>Uncharged, non polar</td>
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<tr>
<td>(vander Waals)</td>
<td>Any clay with oxygen surfaces (e.g. kaolinite)</td>
<td>(e.g. aromatic, alkyl C)</td>
</tr>
<tr>
<td>Hydrogen bonding</td>
<td>Aluminosilicate edge sites, Fe and Al oxides, allophane, imogolite</td>
<td>Amines, carboxyl, carboxyl, phenyhydroxyl, heterocycle N)</td>
</tr>
<tr>
<td>Protonation</td>
<td>Aluminosilicate edge sites, Fe and Al oxides, allophane, imogolite</td>
<td>Amines, heterocycle N, Carbonyl, Carboxylate.</td>
</tr>
<tr>
<td>Ligand exchange</td>
<td>Smectite, vermiculite, illite</td>
<td>Carboxylate, Phenolate</td>
</tr>
<tr>
<td>Cation exchange (permanent</td>
<td>Aluminosilicate edge sites, Fe and Al oxides, allophane, imogolite</td>
<td>Amines, ring NH, heterocyclic N</td>
</tr>
<tr>
<td>charge sites)</td>
<td>Smectite, vermiculite, illite</td>
<td>Carboxylate for anion exchange, amines, ring NH, heterocyclic N</td>
</tr>
<tr>
<td>PH Dependent charge sites</td>
<td>Aluminosilicate edge sites, Fe and Al oxides, allophane, imogolite</td>
<td>for cation exchange</td>
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<tr>
<td></td>
<td>Smectite, vermiculite, illite</td>
<td>Carboxylate, amines, Carbonyl, Alcoholic – OH</td>
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<tr>
<td>Cation bridging</td>
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<td>Water bridging</td>
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Preparation of clay–drug complexe: Clay particles are dispersed in aqueous drug solutions, dispersions are allowed to equilibrate for a suitable time, and finally solid phases are recovered and dried.

- To “entrap” bioactive molecules by inducing coagulation in nanoclay dispersions.
- Dry method (specifically helpful for poorly soluble molecules) was also reported, consisting in grinding the clay and the drug together or putting them in contact at the melting temperature of the drug (Jasra et al., 2006).

Extended-release systems

Clays and clay minerals
Pharmaceutical grade clay minerals (including smectites, kaolinite and fibrous clay minerals) have been extensively applied for prolonged release.

Layered double hydroxides
Synthetic layered double hydroxides (LDH, anionic clays) can also be used as host compounds because of the positively charged layers and the presence of interlayer anions; these compounds are especially helpful for retention of negatively charged biomolecules.

Modified clays
In the development of claybased extended release formulations, modulation of the properties of the clay mineral (specific surface area, porosity, hydrophilic character, kind of exchangeable cations) may be needed to improve its affinity with the bioactive molecules (Okmoto et al., 2003, LeBaron et al., 1999).

Site-specific systems
Colon targeted systems
Site-specific drug delivery to the colon is attracting increasing attention, both for therapy of colon-related diseases as well as systemic drug delivery. Attempts to develop a novel oral delivery formulation of 5-fluorouracil, by using montmorillonite as slow release vehicle for the treatment of colon-rectal cancer are in place. LDH loaded with the anti-inflammatory fenbufen and coated with Eudragit® S 100 or Eudragit® L 100 (to prevent gastric release) provided promising in vitro release profiles for colon targeted administration (Morgan et al., 2007).

Periodontal systems
The suitability of two tetracycline loaded laminar clay minerals as novel products in the site specific treatment of periodontitis were investigated.

Hydration-activated extended release systems
Smectites successfully act as disintegrated agents in tablet formulations because of their hydrophilic and swelling properties. Extended-release tablets by direct compression of sodium sulphatiazole and magnesium aluminum silicate (30% wt/wt) shows progressive formation of a viscous gel layer around the tablets during in vitro dissolution tests. In this test drug release was not significantly affected by tablet hardness but increased with rising stirring rate.

Particulate delivery systems based on clay minerals
Microparticles recently patented modulated release microparticulates for administration of macromolecules into lungs, containing silicates (e.g., amorphous silica, bentonite, attapulgite, kaolin and talc) as the encapsulating agents both for protecting the active substance and modulating release into the body. Pharmaceutical nanoparticles are often made of organic polymers (biodegradable or not) but inorganic systems are receiving much attention in the pharmaceutical field. In particular, clay minerals can provide spontaneous submicron dispersions in aqueous media, resulting in low cost and biocompatible systems with large surface area and high inclusion capacity. Polymer/clay nanocomposites are a new class of hybrid systems in which inorganic or organo-clay nanoparticles (often montmorillonites) are dispersed in a polymer matrix. They have some interesting advantages compared to the pure polymer, such as enhanced mechanical and rheological properties. These benefits along with the good intercalation capacity offered by the clay mineral particles have been used to develop new controlled release systems, as documented by a number of patents (Park et al., 2003, Ochi et al., 2006).

Polymer/layered silicate nanocomposites have attracted great interest, both in industry and in academia, because they often exhibit remarkable improvement in materials properties at very low clay content (3–6 wt %), when compared with virgin polymer or conventional composites. Three methods have been developed to produce polymer/layered silicate nanocomposites: in situ polymerization in which a polymer precursor or monomer are inserted in between clay layers and then expanding the layered silicate platelets into the matrix by polymerization. This method has the advantage of producing well-exfoliated nanocomposites and have been applied to a wide range of polymeric systems; solution-induced intercalation method involves solvents to swell and disperse clays into a polymer solution and melt processing method applies intercalation and exfoliation of layered silicates in polymeric matrices during melt In addition to these three major processing
methods, other fabrication techniques have also been developed. These include solid intercalation, sol–gel method, and the sol–gel method. The structure of polymer/layered silicates composites has typically been established using wide angle X-ray diffraction analysis and transmission electron micrographic observation (Serizawa et al., 2006).

Rheological modifier

Rheological modifiers control the flow properties of liquid systems such as paints, inks, emulsions or pigment suspensions by increasing the medium viscosity or impart thixotropic flow behavior to liquid system.

Good color retention and coverage for nail lacquers, lipsticks and eye shadows. They have been tested to be nonirritant for both skin and eye contact the applicability of organoclays as rheological modifiers in paints, inks, grease and cosmetics (Zhou et al., 2004).

Nanoclay as drug vehicle

The continuous development of new controlled drug delivery systems is driven by the need to maximize therapeutic activity while minimizing negative side effects. One class of drug delivery vehicle that has received more attention in recent years is layered materials which can accommodate polar organic compounds between their layers and form a variety of intercalated compounds. Because the release of drugs in drug-intercalated layered materials is potentially controllable, these new materials have a great potential as a delivery host in the pharmaceutical field. Calcium montmorillonite has also been used extensively in the treatment of pain, open wounds, colitis, diarrhea, hemorrhoids, stomach ulcers, intestinal problems, acne, anemia, and a variety of other health issues. Not only does montmorillonite cure minor problems such as diarrhea and constipation through local application, it also acts on all organs as well montmorillonite nanoparticle drug delivery system, formulating the drug carrier from a material, which can also have therapeutic effects, either synergistic with or capable to mediate the side effects of the encapsulated drug. Paclitaxel (anticancer drug)-loaded poly (D, L-lactide-co-glycolide)/montmorillonite nanoparticles were prepared by the emulsion/solvent evaporation method and was tested for in vitro drug release. The initial burst of 22% on the first day can be observed for sample. After that, the release of paclitaxel was at a slow constant rate. In three weeks, about 36% drug was released with a slightly reduced initial burst and speed release (Vaia et al., 1996).

The adsorption and desorption of organic molecules and surfactants on layered silicates indicates that these materials can be used for drug delivery. The release of buformin from buformin/montmorillonite complex and pure buformin hydrochloride in artificial intestinal juice over 360 min. Buformin/montmorillonite complex released 70% of buformin with lower rate as compared to pure compound in 360 min Medical devices such as a drug delivery patch, implantable or insertable medical device comprise of polymer carrier (as matrix) and drug intercalated layered silicates (as reinforcement) provides controlled release of therapeutic agent to damaged cell of a patient In addition to surface unmodified and modified montmorillonite, layered double hydroxides are also used as drug carrier in various applications. Intercalation of fenbufen in a layered double hydroxide followed by coating with Eudragit® S 100 gives a composite material which shows controlled release of the drug under in vitro conditions which model the passage of a material through the gastrointestinal tract Intercalations of anti-inflammatory drug in layered double hydroxide have the advantage of gradual release over a longer period of time Gene therapy is gaining growing attention for the treatment of genetic deficiencies and life-threatening diseases. For the efficient introduction of foreign DNA into cells, a carrier system is required. Recently, it has been successfully demonstrated that novel layered double hydroxide could form a nanohybrid by intercalating with bimolecular anion such as mononucleotides, DNA which shows that antisense oligonucleotide molecules packaged in the layered double hydroxide can enter cells, presumably through phagocytosis or endocytosis. The leukemia cells were used to explore the layered double hydroxide’s potential as gene carriers (LeBaron et al., 1999).

Clay miner also used to improve drug dissolution rate

Improving dissolution of poorly water-soluble drugs remains one of the more important challenges for pharmaceutical technologists. Among the several approaches applied the surface adsorption of drug (Gordon et al., 2007) is one interesting approach. Molecules onto finely divided solids greatly increase the surface area available to the dissolution medium. Smectites were found to effectively enhance the in vitro dissolution rate of non-ionic and acidic insoluble drugs. Drug release from the clay surface is promoted by the weak bonding between them and concomitantly drug wettability is enhanced due to the hydrophilic properties of the clay. Phenytoin-montmorillonite adsorbates were able to improve the bioavailability of the drug in humans in comparison with phenytoin sodium capsules (Yuanichi et al., 2001).
Conclusion

Nanoclay as drug vehicle for controlled release of drug is one of the born age area in medicinal application. Nanoclays have great potential as compared to polymer and carbon nanotubes for drug delivery applications. The investigation of clay–drug interaction and release mechanisms is an essential contribution for the formulation of clay-based drug delivery systems.

References


