Clay and Polymer-Based Composites Applied to Drug Release: A Scientific and Technological Prospection.

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Abstract - There has been a growing trend in recent years for the development of hybrid materials, called composites, based on clay and polymers, whose innovative properties render them attractive for drug release. The objective of this manuscript was to conduct a review of original articles on this topic published over the last decade and of the body of patents related to these carriers. A scientific prospection was carried out spanning the period from 2005 to 2015 on the Web of Science database. The technological prospection encompassed the United States Patent and Trademark Office, the European Patent Office, the World International Patent Office and the National Institute of Industrial Property databases, filtering patents with the code A61K. The survey revealed a rise in the number of publications over the past decade, confirming the potential of these hybrids for use in pharmaceutical technology. Through interaction between polymer and clay, the mechanical and thermal properties of composites are enhanced, promoting stable, controlled drugs release in biological media. The most cited clays analyzed in the articles was montmorillonite, owing to its high surface area and capacity for ion exchange. The polymeric part is commonly obtained by copolymerization, particularly using acrylate derivatives. The hybrid materials are obtained mainly in particulate form on a nanometric scale, attaining a modified release profile often sensitive to stimuli in the media. A low number of patents related to the topic were found. The World International Patent Office had the highest number of lodged patents, while Japan was the country which published the most patents. A need to broaden the application of this technology to include more therapeutic classes was identified. Moreover, the absence of regulation of nanomaterials might explain the disparity between scientific and technological output.

INTRODUCTION

Fast and immediate release pharmaceutical forms are the most commonly sold. However, in some situations their use is associated with high frequency of administration and irregular plasma concentration, which in turn can lead to adverse effects or poor efficacy. This situation has prompted efforts to develop systems that provide controlled release of active substances. This objective can be attained by combining production technologies and pharmaceutical excipients (1).

A variety of excipients are available on the market where polymers are commonly used in conventional pharmaceutical formulations as coatings, suspending agents, surfactants, binders, among others (2). However, they also act as stimulus-responsive carrier matrices able to regulate the release of active principles in biological media (3). Despite their biocompatibility and biodegradability, polymers have some shortcomings with regard to their functionalities which need improvement such as thermal degradation behavior under lower temperatures, low tensile strength, and initial burst effect (4–8). To this end the generation of hybrid materials, also referred to as composites, has become common (9).

A composite is a dispersion constituted by two or more components with optimized properties compared to the pure materials. When the composite has nanometric scale in at least one dimension, this system can also be considered a nanocomposite. These hybrid materials can be obtained by incorporating the polymer into clay layers or channels or by dispersing platelets of the inorganic composite into the polymeric matrix (10).

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This association is of interest because natural clays are abundant, low cost and the amount of clays required to obtain significant modifications in the polymer matrix is greatly reduced (11). In addition, clays offer barrier properties that hinder the diffusion of host molecules. This feature is interesting when the goal is to develop a modified release system (12).

The association of clay-minerals and polymers modifies drug release profile, generally making it prolonged. It increases solubility of the active ingredients, and confers better mechanical and thermal properties to the composite (13–17). All these characteristics are strongly dictated by the surface area and ion exchange capacity of the clay, by the types of interactions between the elements involved, and the clay/polymer ratio (18).

In view of the versatility of clay-polymer composites, the objective of the present manuscript was to conduct a review of original articles on the topic published over the last decade and of the body of patents related to these carriers, determining the organic-inorganic associations found on search, interactions, systems obtained and analyses performed, and finally addressing the advantages attained by the use of polymer-clay composites for therapeutic purposes.

METHODOLOGY

This study was based on a search of original articles, available in full, published in the past 10 years (2005 to 2015) in English, conducted in May 2016. The descriptors employed were "composite", "nanocomposite", "clay", "polymer" and "drug release", searched in the title, key words or abstract. Review articles and documents not pertinent to systems comprising polymers and clays for drug release, or that with an exclusively diagnostic, clinical, epidemiologic, microbiologic, tissue engineering, toxicological and/or analytical focus, were excluded from this study. The Web of Science database was employed in this study because it held the highest number of publications, excluding the other databases due to repetition of the articles selected.

The search for patents also took place in May (2016), using the terms "composite" or "nanocomposite", "polymer" and "clay" on the United States Patent and Trademark Office (USPTO), European Patent Office (EPO) and World International Patent Office (WIPO) technology databases. The equivalent terms in Portuguese were employed on the National Institute of Industrial Property (INPI) database. These terms were searched in the title and abstract of the documents. The International Patent Classification code A61K (Hygiene Preparations for Medical, Dental, or Toilet Purposes) was used as a filter to further refine selection for studies on drug release.

Scientific Prospection

Clay and polymer-based composites applied as drug carriers

The initial search using the descriptors outlined above led to the retrieval of 109 articles. The articles retrieved were then screened by reading of the abstracts, with the inclusion of articles addressing the application of clay and polymer-based composites as drug carriers. A total of 67 articles were selected for the review at this stage.

The distribution of the selected articles by year of publication is depicted in Figure 1. Growing interest in the topic was evident, with a steady rise in the number of publications up to the beginning of this decade followed by a levelling out, with publications peaking in 2015. Although the number of articles appears to have dipped in 2012 and 2014, some of the articles found for these periods were excluded because their full texts were not available.

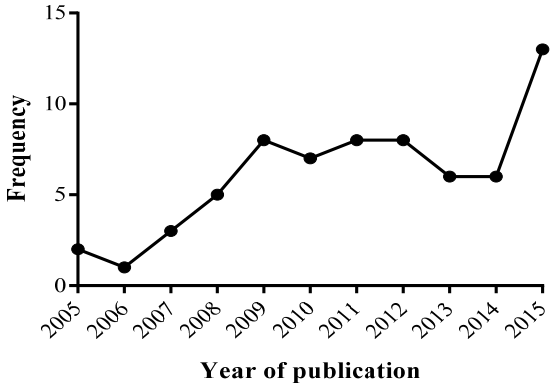

Figure 1. Number of articles on clay-polymer composites published during the period

Interest in the topic can be explained by the major benefits of the pharmaceutical use of composites able to control the release of bioactive molecules, where most conventional excipients adopted do not possess all the properties required to satisfactorily overcome specific limitations. DeLeon et al. developed a nanocomposite based on lamellar double hydroxide (LDH) and poly L-lactic acid for controlled release of ibuprofen. The glassy modulus of the films increased 50-70% with addition of LDH, and the glass transition temperature of the nanocomposites was higher than that of pristine polymer. This indicates improvement of the thermal and viscoelastic properties of the hybrid films. An increase in drug dissolution rate was also observed, which occurred by two distinct mechanisms, diffusion and ion exchange (64). Thus, the characteristics arising from interaction of organic and inorganic materials can be exploited to create efficient and functional release systems, providing stable controlled drug desorption in biological media (10,19).

A nanocomposite is obtained when the polymeric chain is incorporated into layers or channels of the clay, where its formation can be confirmed by changes in the basal space of the clay disclosed on diffractometry (20). Alternatively, the minimum units of clay can also be dispersed into the polymer matrix, with marked increase in interaction between the two, producing a material with different characteristics to the parent constituents (21). These are referred to as intercalated and exfoliated systems, respectively. However, it is noteworthy that these types of dispersions can coexist in the same composite (22,23).

Among the articles assessed, authors endeavored to characterize the composites, expounding on the improvements promoted by the association for drugs release. Most of the composites obtained exhibited change in the resistance of the polymers to tension, with enhanced thermal stability and modulation of the swelling of the polymer in aqueous media (24–26). Nanohybrid poly-ε-caprolactone / hydrotalcite / diclofenac (PCL-HDIC) fibers produced by electrospinning technique showed degradation temperatures higher than the pristine polymer after the addition of hydrotalcite in different proportions (1%, 3%, 5% and 10%), without affecting the crystallinity of poly-ε-caprolactone, as shown in Figure 2 (24).

These characteristics are highly relevant when the hybrid material is developed as a carrier of bioactive substances. Since the new properties of the hybrid material influences the interaction of the composite with the organism, particularly when the composite is designed to be responsive to fluctuations in external factors, such as pressure and temperature.

Analysis of composites show effective change in different properties of the new material relative to the parent polymer and clay, including swelling index, mucoadhesion ability, thermal analysis, mechanical strength, strain modulus and fracture resistance (16,23,26–29). Wu et al. (30) obtained a composite whose mechanical properties were superior to those of polymeric hydrogel. The high viscoelasticity attained by the composite was attributed to structural rearrangement when the gel was under strain, resulting from the interaction of Pluronic F127 with Laponite nanoparticles. The composites included in the present review, together with their respective compositions, are given in Table 1.

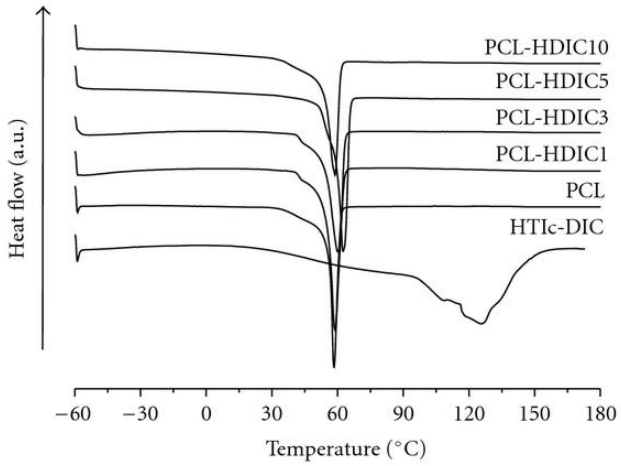

Figure 2. DSC heating scans of pure PCL, HTlc-DIC, PCL-HDIC1, PCL-HDIC3, PCL-HDIC5 and PCL-HDIC10. Reproduced from Ref. 24.

Table 1. Examples of hybrid systems with potential application in drug release systems

Inorganic Part	Polymeric Part	Model Molecule	References
Montmorillonite	Poly (lactic-co-glycolic acid)	Paclitaxel	(31)
		Atenolol	(32)
	Polydimethylsiloxane	Solvent blue 35 dye	(33)
	Polyurethane	Chlorhexidine	(34,35)
		Triamcinolone acetonide	(21)
		-	(4,6)
	Chitosan	Paracetamol, theophylline, two xanthine derivatives, two nitric oxide donors	(36)
		Diclofenac	(37)
		Vitamin B12	(38)
		Doxorubicin Hydrochloride	(14)
	Polylactic acid	-	(5,8)
	Chitosan - Polylactic acid	Ibuprofen	(39)
Montmorillonite	Polyethylene Glycol	Paracetamol	(40)
	Polyvinylpyrrolidone - Ethylene Glycol	-	(7)
	Poly-ε-caprolactone	Paracetamol	(18)
		Ibuprofen	(41)
	Polyethylene and derivatives	Carvacrol	(42)
		-	(43)
	Collagen – Poly(sodium acrylate-co-acrylamide)	-	(44)
	Derivatives of acrylic acid	-	(23,45)
		Caffeine	(46)
		Doxorubicin, methotrexate and ciprofloxacin	(13)
	Polyoxy-propylenediamine	Ibuprofen and theophylline	(47)
	Polyvinyl alcohol	-	(48)
		Gentamicin sulphate	(49)
	Polyisobutylene	Urea hydrogen peroxide	(25)
	Guar gum	-	(22)
	Gelatin - Polyethylene glycol-dimethacrylate	-	(26)
	Polymethylene-polyphenylene-isocyanate	-	(50)
Bentonite	Sodium alginate	Propranolol	(51)
	Polyvinylpyrrolidone	-	(20)
	Derivatives of acrylic acid	-	(15,52)
	Chitosan	-	(28)

Table 1. Continued…

Rectorite	Carboxymethyl chitosan	-	(53)
Attapulgite	Derivatives of acrylic acid	Rhodamine B	(54)
		-	(11)
	Polypyrrole	Acetylsalicylic acid	(55)
Laponite	Chitosan and derivatives	-	(29)
		Vancomycin	(56)
	Pluronic-diacrylate	-	(30)
	Poly (lactic-co-glycolic acid) - Pluronic	Doxorubicin	(57)
	Derivatives of acrylic acid	-	(58–61)
	Sodium alginate	-	(62)
Fluoromica	Polyethylene glycol	Paracetamol	(40)
	Polylactic acid	-	(5)
	Poly-ε-caprolactone	Paracetamol	(18)
		Ibuprofen	(41)
Sepiolite	Polylactic acid	-	(5)
Layered Double Hydroxides	Polylactic acid	Ibuprofen	(63,64)
		-	(8)
	Poly-ε-caprolactone	Benzoate, 2,4-dichlorobenzoate, para-hydroxybenzoate and ortho-hydroxybenzoate	(65)
		Diclofenac	(24,66)
		-	(16)
	Polyvinylpyrrolidone	Ibuprofen, acetylsalicylic acid, naproxen	(67)
	Derivatives of acrylic acid	Diclofenac	(17,68)
Halloysite	Poly (lactic-co-glycolic acid)	Tetracycline hydrochloride	(69)
		Thymol(2-isopropyl-5-methylphenol)	(70)
	Sodium alginate	Diclofenac	(71)
	Chitosan	Rhodamine 110 chloride and 5(6)-carboxyfluorescein	(72)
	Hyaluronic acid	Rhodamine 110 chloride and 5(6)-carboxyfluorescein	(72)
	Ethoxysilane derivative	Ibuprofen	(73)
Vermiculite	Carboxymethylcellulose	Chlorhexidine	(74)

Legend: (-) No model molecule was incorporated into the composite.

Just over half of the articles (58.2%) reported the behavior of the hybrids as carriers of bioactive molecules in experimental release models, whereas the focus of the others was on the obtention and characterization of the composites. Notably, a smaller proportion of the studies (19.4%) assessed the composites using *in vitro* models based on cytotoxicity assays, adhesion ability and cellular absorption, and also antimicrobial assessment (4,13,35,37,56,62,74).

The main drugs carried in the articles analysed were non-steroidal anti-inflammatory drugs (46.1%) (24,39,40,66–68), antimicrobial (25.6%) (21,34,65,69,74) and chemotherapeutic agents (10.3%) (13,14). This distribution can be explained by the adverse events associated with the use of

these active principles, whether due to the reduction in gastric protection resulting from prolonged use of the anti-inflammatory drugs and analgesics, or to the intrinsic toxicity of chemotherapeutic agents and some antimicrobials associated with the risk of resistance (75,76).

Feng et al. (2009) developed nanoparticles based on PLGA, vitamin E derivative (TPGS) and montmorillonite (PLGA-TGPS/MMT NPs) for the release of docetaxel, a chemotherapeutic with low oral bioavailability. Addition of this clay in the formulation can be justified by the gastroprotective effect, by the adsorption capacity that allows the controlled release of drugs and by the mucoadhesive properties that favor the absorption of the nanoparticles. The pharmacokinetic profile of formulations evaluated in an animal model, showed 78% bioavailability of docetaxel PLGA-TGPS/MMT NPs in comparison with 3.59% for the Taxotere® (oral formulation). It was possible to increase the bioavailability of docetaxel and extend its half-life (from 6.9 h to 118.8 h), achieving sustained release of the drug. This would imply a change in the frequency of administration of 22 hours (intravenous formulation) to 3 weeks (oral formulation), avoiding fluctuation in plasma levels of the drug, making oral administration possible and shorten the need for hospitalization (77).

The active ingredient mostly reported in the selected articles in this search was Ibuprofen, which was assessed in different composites including chitosan-poly (L-lactic acid)/montmorillonite (39); poly-ε-caprolactone/montmorillonite and fluoromica (41); polyoxypropylene/montmorillonite (47); polylactic acid/layered double hydroxides (63,64); triethoxysilane and octylethoxysilane/halloysite (73). This drug has low solubility and short half-life, characteristics that are suitable for the use of delivery systems that modulate these drawbacks.

Clays

Clays are a material widely available in many parts of the world, constituted basically by aluminum and magnesium silicates. The main characteristics of clay are defined by the arrangement and proportion of octahedral and tetrahedral sheets, isomorphic substitutions that determine their charge, and also by particle size and ion exchange capacity (78).

The clays cited in the articles analyzed are depicted in Figure 3. Some articles comparatively assessed distinct clays or the same clay modified by different processes (5,18). Although Lamellar Double Hydroxides (LDH) are not clays, their lamellar structure and intercalation properties have made these solid materials of great interest in the pharmaceutical industry, being generally referred to as anionic clays (79). Therefore, the authors included the LDH-related articles retrieved in the search in this review. Clays cited only once were grouped under the "Others" column, and included sepiolite, rectorite and vermiculite.

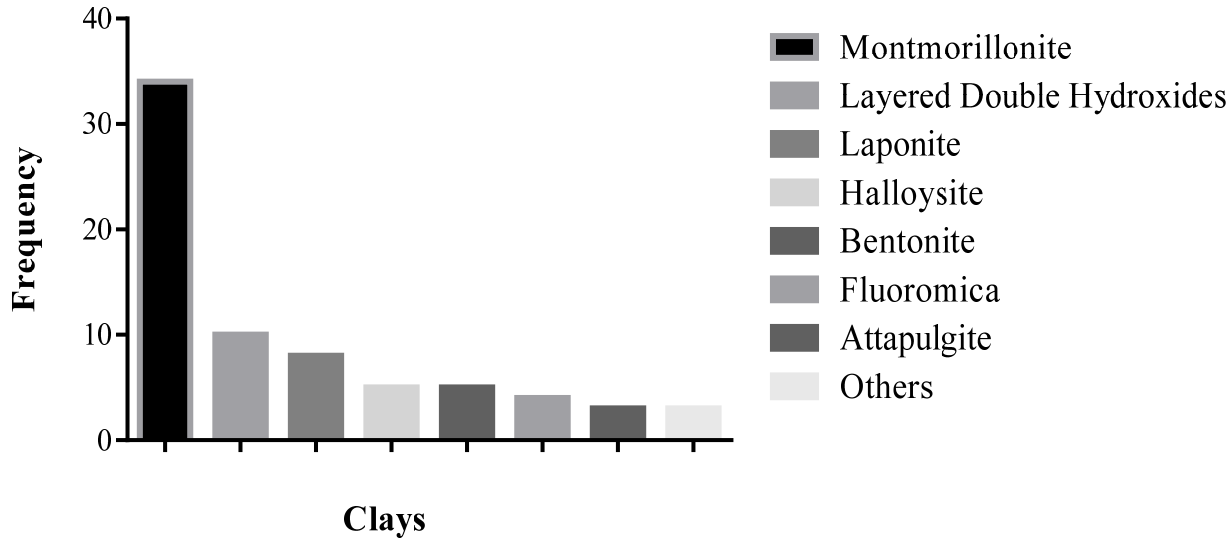

Figure 3. Frequency of clays employed in hybrid systems in the articles analysed between 2005 and 2015.

Table 2. Characteristics of clays cited in this paper.

Clay Minerals	Group	Layout	Chemical Formule
Montmorillonite	Smectite	Lamellar	$(Na,Ca)_{0,3}(Al,Mg)_2Si_4O_{10}(OH)_2 \cdot nH_2O$
Bentonite	Smectite	Lamellar	$Na_{0.5}Al_2(Si_{3.5}Al_{0.5})O_{10}(OH)_2 \cdot n(H_2O)$
Laponite	Smectite	Lamellar	$Na_{0,3}(Mg,Li)_3Si_4O_{10}(F,OH)_2 \cdot nH_2O$
Rectorite	Smectite / Mica	Lamellar	$(Na,Ca)Al_4(Si,Al)_8O_{20}(OH)_4 \cdot 2H_2O$
Fluoromica	Mica	Lamellar	$Na_{2x}Mg_{3.0-x}Si_4O_{10}(F_yOH_{1-y})_2$ ($x = 0.33$, $y = 0.98$)
Vermiculite	Vermiculite	Lamellar	$Mg_{0.7}(Mg,Fe,Al)_6(Si,Al)_8O_{20}(OH)_4 \cdot 8H_2O$
Halloysite	Kaolinite - Serpentine	Tubular	$Al_2(Si_2O_5)(OH)_4$
Attapulgite	Sepiolite - Palygorskite	Fibrous	$Mg(Al_{0.5-1}Fe_{0-0.5})Si_4O_{10}(OH) \cdot 4H_2O$
Sepiolite	Sepiolite - Palygorskite	Fibrous	$Mg_4Si_6O_{15}(OH)_2 \cdot 6H_2O$

Table 2 represents the main characteristics of the clays referenced in this review. Clays listed have negative surfaces of variable charge, among which laponite, halloysite and fluoromica are of synthetic origin. Among these clays, bentonite/montmorillonite, laponite, sepiolite (Magnesium trisilicate) and attapulgite (also known as palygorskite) are considered excipients and have monographs in pharmaceutical compendia, such as the United States Pharmacopeia, European Pharmacopoeia and Handbook of Pharmaceutical Excipients. These raw materials are very functional and can be used as suspending agents, emulsifying agents, gelling agents, adsorbents, and glidants in pharmaceutical formulations. Aluminum and magnesium silicates are also used for therapeutic purposes, mainly intended for the disorders of the gastrointestinal tract (80).

Lamellar double hydroxides were not included in the table because they have a very diverse chemical composition, in addition they are not actually clays, although they have a structure similar to brucite. Great pharmaceutical interest in this material is due to simplicity of the synthesis technique, its lamellar character and the surface charge. Its structure allows the intercalation of organic molecules, especially those negatively charged, since the substitution of divalent cations by trivalents occurs, yielding positively charged sheets (81).

Pharmaceutical use of clays requires that their chemical and mineralogical composition, stability and toxicity are well defined. Because of their origin and adsorbent characteristics, these materials can be contaminated by elements present in the soil such as arsenic, lead, strontium, barium, among others, which are not allowed or are tolerated only at extremely low concentrations in medicinal products (82). Administration of medicines based on pharmaceutical grade clays is generally restricted to oral or topical route, and there are no reports of absorption of these materials through the mucosa. Absorption phase only occurs for the ions that are present in the clays (83,84). However, it should be emphasized that the presence of quartz in natural clays is very common and the accumulation of this element in the airways causes irritation, which may restrict the pulmonary application of clay-based composites (80).

Figure 4 demonstrates the cytotoxic effect of Poly(lactide-co-glycolide)-laponite-F68 nanocomposite vesicles (PNC) on L929 cells in a concentration-dependent manner. Cell viability ranged from 97.88% to 91.62% for vesicles without the drug at concentrations of 1 and 5 mg/mL, respectively. For doxorubicin-loaded vesicles the cell viability for the concentrations of 1 and 5 mg/mL were 57.19% and 37.52%, respectively. Therefore, nanocomposites without doxorubicin had viability similar to the negative control (M), corresponding to the incubation medium, indicating the absence of cytotoxic effect of the carrier (57).

Several studies demonstrate the biocompatibility of clays and their respective composites. The toxicology study of montmorillonite was conducted in vivo by administering oral and intravenous doses of 142.9 mg/kg and 14.29 mg/kg, respectively, in Winstar rats. After 72 hours samples were collected for biochemical, hematological and histopathological exams, indicating that there were no pronounced differences in relation to the control group, except for the small reduction of some electrolytes and a slight increase of Kupffer cells in the liver (85). Halloysite showed no toxic effect at concentrations below 100 μg/mL in human cell lines MCF-7 and HeLa, with approximately 70% viable cells (86). The carcinogenicity of attapulgite was studied in vivo and in vitro models. Balb/c mice had the clay administered intraperitoneally twice weekly for 5 weeks and the results demonstrated that attapulgite is non-carcinogenic, unlike other toxic fibrous silicates, such as asbestos (87).

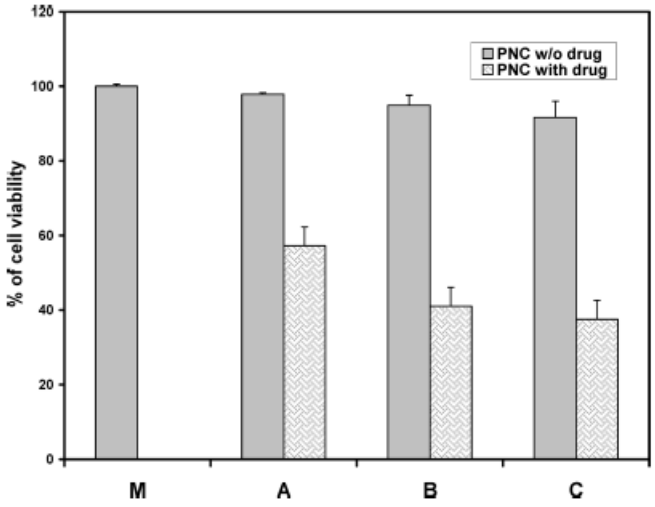

Figure 4. Cytotoxicity of bare and doxorubicin-loaded PNC vesicles on L929 cells after incubation with different concentrations (A, 1 mg/mL; B, 2.5 mg/mL; and C, 5 mg/mL) for 24 h. Reprinted with permission from Ref. 57. Copyright, 2012, American Chemical Society.

An study conducted by Depan et al. (2009) employing natural montmorillonite associated with chitosan-poly(L-lactic acid) showed that cellular viability in fibroblast cultures was unaffected, confirming the biocompatibility of the composite (39). Styan et al. (2008) demonstrated the cytotoxic effect of organophilized montmorillonite composites in an *in vitro* model using fibroblasts. The toxic effect was attributed to the release of the organic modifier from the nanoparticles, given the interaction of the cationic chain of quaternary amine with the cellular membrane (6).

Sharma et al. (2014) evaluated the toxic effect of organomodified montmorillonite (Cloisite® 30B) by oral administration of two single doses of 250, 500 and 1000 mg/mL in rats for 24 hours apart. Although studies of this group have previously shown the genotoxic effect of this clay, in vitro, results of the comet assay performed on cells collected from the liver, kidneys and colon of animals previously treated with Cloisite® 30B were not significant in relation to the animals treated with water, indicating that this excipient is not genotoxic *in vivo*. In addition, analysis of feces and organs indicated that there was no absorption of aluminum, constituent element of Cloisite® 30B, and therefore, after oral administration there was no systemic exposure of clay (88).

In this research, the clay of most interest was montmorillonite, possibly due to the numerous benefits inherent to this clay-mineral. Montmorillonite is a smectite of natural origin whose use for pharmaceutical purposes has been approved by regulatory agencies of a number of countries. This clay has a high interaction capacity due to its large surface area provided by a lamellar structure. It also has a high ion exchange capacity compared to other clays. However, under physiological conditions, in solution of electrolytes, montmorillonite tends to precipitate. Consequently, the preparation of a composite can stabilize the clay in biological media (13).

The montmorillonite employed in composites is generally organophilized by changing its surface with organic cations that have surfactant properties (6,49). This alteration is applied mainly in cases where the bioactive molecule and/or polymer is hydrophobic, hampering the development of a stable composite. In addition, the chemical modification induces enlargement of the distance between the platelets of layered clays, such as smectites or layered double hydroxides, or of the lumen of halloysite. This structural change can be sufficient to increase the adsorption capacity of the clay, increasing the proportion of drug adsorbed onto its surface (47,73).

Liu et al. (2008) added montmorillonite to chitosan to control the release rate of vitamin B12 via electrostimulation, showing the ability to maintain responsiveness to successive stimuli. Controlled release of the vitamin was modulated by the proportion of clay in the composite, whose increase formed a denser hydrogel and limited the diffusion of the bioactive molecule. The nanocomposite exhibited a stable release profile after 10 cycles of stimuli. An improvement over results achieved with chitosan hydrogel (38).

Another inorganic material frequently cited in the selected articles was the synthetic smectite Laponite, which is biocompatible, non-toxic and

has nanometric lamellar structures. Its surface is negatively charged, facilitating interaction with polymers and cationic drugs (62). The chitosan and Laponite film developed to release the antibiotic vancomycin promoted retention and sustained dissolution of the drug for longer than with chitosan alone. This result can be explained by electrostatic interaction between the polymer and clay, which formed a dense chain with a controlled rate of swelling, restricting the release of vancomycin (56).

Polymers

Drug delivery systems allow an active ingredient to reach the target site at the proper therapeutic concentration. The most commonly used drug excipients are polymers, long organic chains formed by repeated units. Polymeric carriers can be employed to protect the drug, increase its bioavailability, or modify its release. These carriers must provide biocompatibility, biodegradability, swelling capacity, among other characteristics.

There are several composites derived from polymer blends and copolymers mentioned in the literature for drug delivery, however the addition of clays in the organic matrix may induce superior effect on some parameters. Xiang et al. observed the effect of the addition of attapulgite on the characteristics of hydrogel obtained by in situ polymerization of acrylates and polyethylene glycol radicals. Swellability of the hydrogel increased approximately fivefold when the concentration of clay was 0.05% in the composite. This same composite exhibited increased tensile strength and elongation capacity relative to the amount of attapulgite added to the hydrogel, since clay guides the direction of elongation and its crosslinking action prevents the formation of fractures under tension (11).

The distribution of polymers in the composites reported in the articles selected by this review is depicted in Figure 5. Polymers or copolymers cited only once were placed under “Others”.

A host of different constituents were used in the polymeric part of these hybrid materials, ranging from chitosan (14,28,36–38,56,72), alginate (51,62,71), guar gum (22) and hyaluronic acid (72), to synthetic polyvinyl alcohol (48,49), poly (lactic-co-glycolic acid) (32,57,69), polyurethane (4,6,21,34,35), and poly(L-lactic acid) (5,8,63), among others. These polymers were employed predominantly as matrices (22,26,32,35,49,66,74,89), but in some cases formed the composite coating (64,70,71).

The interaction of the polymeric matrix with the inorganic part can allow greater control of the dispersion of the loaded drugs and provide uniformity of the composite by intercalation of the monomers and their subsequent polymerization, a technique known as *in situ* polymerization (90). *In situ* electropolymerization of polypyrrole monomers over palygorskite and acetylsalicylic acid generated a nanocomposite composed of an external polymeric layer. This structure favored the release of the content by electrical stimulation which changed the redox state of the polypyrrole (55).

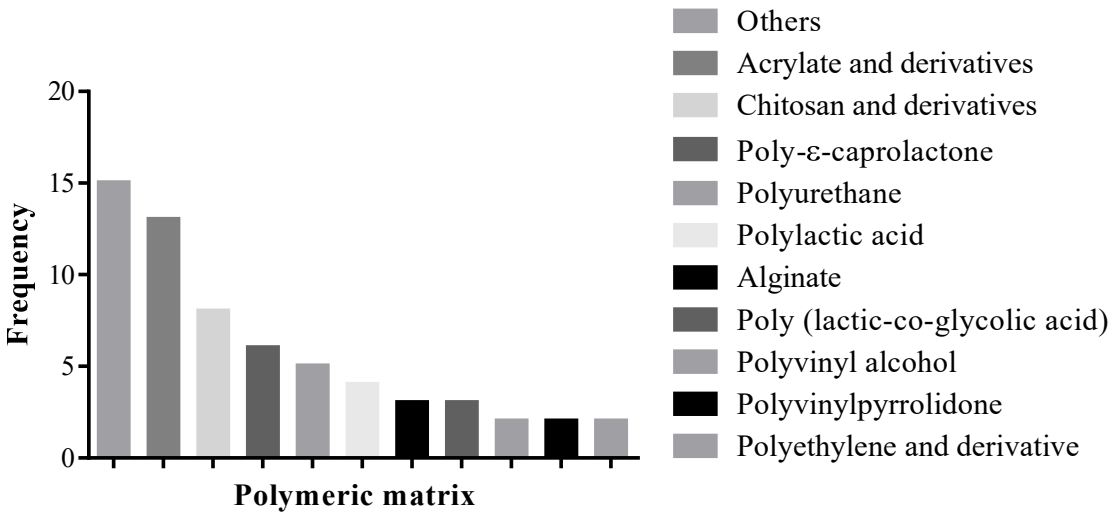

Figure 5. Frequency of organic matrix type used in articles selected

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The use of copolymers in the preparation of the composites was recurrent in the studies found (11,29,52,55,58,60,61). The copolymers associate different polymer units, achieving synergistic effects for certain properties or associating different characteristics. Some polymeric phases were obtained by grafting, a method entailing modification of the polymer surface by covalent bonding of fragments of another polymer (45,61). This process requires stimuli to start copolymerization, such as free radical-forming oxidant agents, ultraviolet light or radiation (91). This was exemplified by Dadkhah et al. (2014) that, through copolymerization of polyacrylamide with monomers of maleic acid, obtained an anionic hydrogel whose swelling can be modified by pH. This type of matrix can be useful for delayed drug release. Given that ionization of copolymer occurs only in alkaline medium, the chains are subject to repulsion with swelling of the matrix and release of the active ingredient only after reaching the intestinal region (46).

With regard to the use of a single organic matrix, greater emphasis was given to acrylates, which are employed preferentially in hybrids whose clay surface has a positive charge. Negatively charged clays, however, also form composites with cationic derivatives of acrylic acid. Despite the wide application of this polymer in pharmaceutical formulations, it shows the initial burst effect. Some examples of improvements in the biopharmaceutical properties achieved with the incorporation of clays in these matrices are mentioned below.

Composite montmorillonite/PLGA have higher mucoadhesion due to the presence of clay and thus greater ability to permeate the mucosa of the gastrointestinal tract. In vitro release studies demonstrate a slight reduction in the immediate release of paclitaxel from hybrid nanoparticles (18%) compared to nanoparticles without montmorillonite (22%) (31). Montmorillonite/PLGA composites also demonstrated prolonged gastric retention time with considerable stability in acidic medium. This implies a greater absorption and bioavailability of the test drug (atenolol), which has low solubility in the lower intestine. The drug dispersed in the polymer matrix had a rapid release of 32% of the drug in the initial 0.5 h in the simulated gastric fluid (pH 1.2), while the montmorillonite/PLGA composite released only 4% of the drug in the same range of time. New release profile favors the treatment of arterial hypertension with a reduced initial release of the drug that is also extended. This change reduces the frequency of administration for chronic therapy, improving patient compliance (32).

Another demonstration of modification in the release profile, can be seen in Figure 6, which represents the in vitro release of the antibiotic tetracycline hydrochloride (TCH) from halloysite (HNT)/PLGA nanofibers, as well as PLGA and clay (HNT) pristine. Tetracycline is bound primarily on the surface of halloysite by electrostatic interactions and only a small amount is inserted into its lumen, and both the clay and the drug are covered by PLGA. Tetracycline/halloysite/PLGA composite (TCH/ HNTs/PLGA) showed sustained release with 32% dissolution of the drug after 28 hours, while 83.8% had been released from the polymer matrix after 24 hours (69).

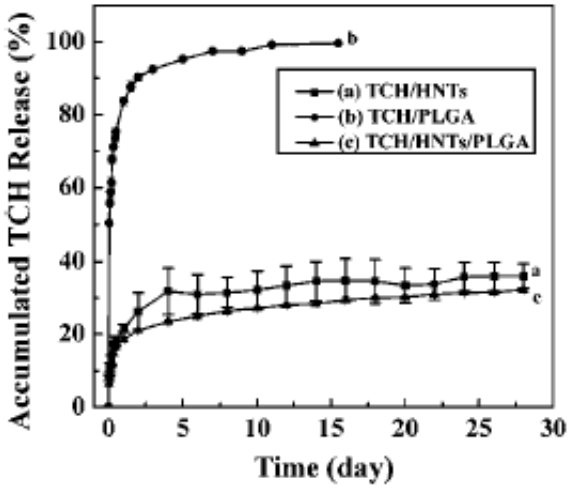

Figure 6. *In vitro* release of TCH from TCH/HNTs powders and electrospun TCH/PLGA and TCH/HNTs/PLGA nanofibrous. The samples were incubated in phosphate buffer (pH = 7.4) at 37°C. Reproduced from Ref. 69 with permission from The Royal Society of Chemistry.

Systems obtained from polymers and clays

The hybrid materials cited in the articles were classified into system types, grouped according to the names attributed by the authors of the article. The systems classified under "Others" were cited only once and include the composites in the form of adhesive, suspension and pellets. There were a high number of particulate systems, predominantly on the nanometric scale (Figure 7).

Of the particulate systems, nanoparticles were the most reported. This result may have been due to reduction of collateral effects, improved attainment of the therapeutic target, solubility and stability, where these represent important characteristics achieved by reducing the size of the carrier (13,92). Nanoparticles of atenolol in PLGA and montmorillonite promoted sustained release of the drug compared to the commercial presentation with conventional release. The composite had prolonged stability in stomach media, leading to greater absorption and bioavailability (32).

The second-most-common materials in the search were hydrogels, consisting of a three-dimensional reticulated polymeric network able to absorb a large volume of water (29,44,93). Given their depot effect, the soluble substances retained can diffuse in a controlled manner, dictated by the degree of reticulation of the matrix and solubility of the drug carried.

Although studies involving hydrogels have been available since the 1950s, the incorporation of inorganic materials to compose them offers a solution to conventional limitations (94). This is because chemically cross-linked hydrogels have poorer mechanical properties (low fracture toughness) and poor stability compared to composites reticulated by clays. These disadvantages are mainly attributed to the restricted molecular movement of the polymer chain due to the large number of random cross links in covalently bonded polymeric hydrogels (11,48).

The clays incorporated into hydrogels act mainly as reticulates, as observed in the alginate, halloysite and hydroxyapatite composites produced by Fan, Zhang and Wang (2013). Electrostatic interactions between the polymer and clay prolong the maximum swelling time of the composite compared to the polymeric hydrogel. The greater density of the system restricts the mobility of alginate, increasing the encapsulation efficiency of the drug and controlling its release (71).

Besides particles and hydrogels, films also have broad application in the development of modified release systems, whether in medical devices with preventive action, mucoadhesion release systems or in coatings (15,35,74). Saha et al. (2014) prepared polyurethane and montmorillonite-based chlorhexidine films and nanofibers. The film promoted release of the drug for up to 200 hours, whereas the nanofiber had fast initial release, possibly due to the greater surface area and porosity of this composite (35).

Modified drug release systems: improvements derived from organic-inorganic interaction

Chien and Lin (2002) classified controlled release systems under three main groups based on the technology approach used, namely: programmed release systems; modulated activation systems; and retrostimulated release systems. Among the systems analyzed in the articles selected, some used modulated release, i.e. exposure to a chemical, physical and/or biochemical stimulus is required for release to be triggered and regulated (96). The main types of stimuli reported in the articles, together with their respective references, are depicted in Figure 8.

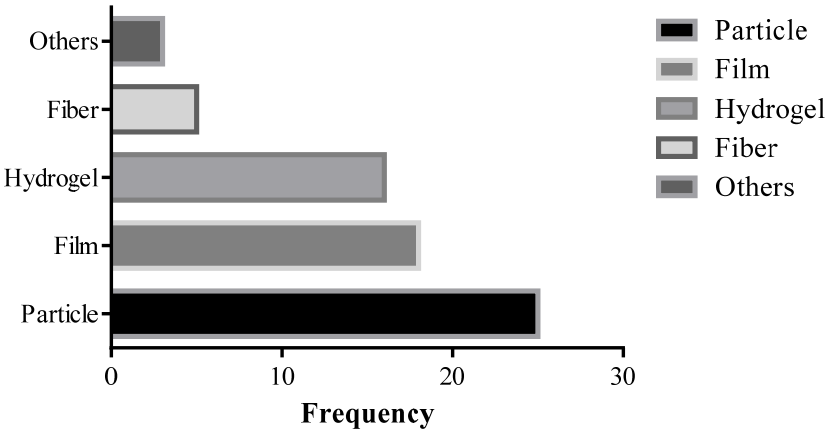

Figure 7. Type of clay-polymer systems by citation frequency in articles.

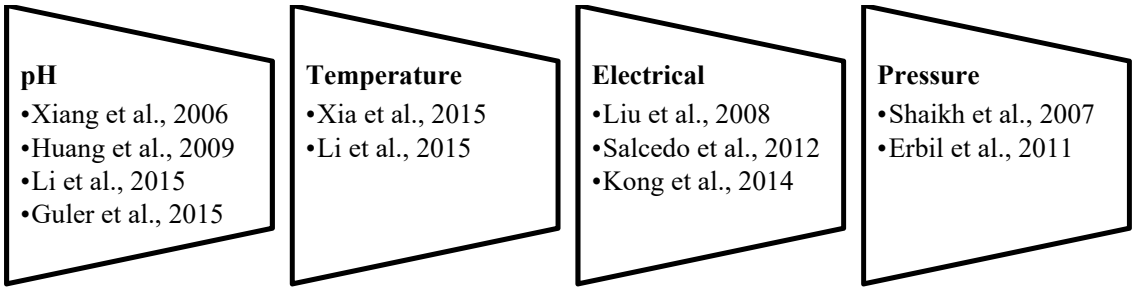

Figure 8. Examples of stimulus-responsive composites.

A number of studies reported pH-sensitive hybrid materials, such as the halloysite and organosilane nanocomposite. In this case, modification to the clay nanotubes promoted sustained drug release. Because the system without hydrophobic polymer layer was well adjusted to the first order kinetics and after modification of the nanotube surface, a Fickian diffusion mechanism was observed. This change was promoted by hydrogen and electrostatic bonds between the drug and clay surface, yielding greater dissolution at pH 7.4 (60% release in 60 hours), probably owing to the solubility of the drug by repulsion of the charges of the active ingredient and carrier in this medium (73).

Another pH-responsive composite comprising palygorskite and poly(2-(diethylamino)ethyl methacrylate) used the clay as emulsifying agent. Microspheres obtained increased in size by reduction of pH (30% after adjusting the pH from 10 to 2) due to repulsion of the protonated amine groups from the polymer in acid medium rendering the matrix less reticulated. Microspheres released 90% of the host molecule after 30 minutes in an acid medium, with full release after 8 hours. On the other hand, at pH 5, 7.4 and 10 the release of rhodamine B was 80, 56 and 37%, respectively, after 8 hours fitting to the Higuchi model. In this case, the sustained release of rhodamine B from microspheres was controlled by diffusion, influenced by pH (54).

Dispersions of polyethylene glycol derivatives in the presence of Laponite nanoparticles were prepared using the *in situ* polymerization method. This nanocomposite is more compact and porous than the chemically crosslinked hydrogel, with equilibrium swelling/deswelling ratio and water retention modulated by composition (proportions of each monomer, polymer concentration and amount of clay) and external temperature. Swelling equilibrium ratio of the hydrogel containing 5 wt% montmorillonite was four times higher than the organic hydrogel, and equilibrium reestablishment with increasing temperature does not occur immediately, suggesting the application of this system for slow release of drugs. Therefore, the physically crosslinked hydrogel by Laponite proved suitable for biological applications given its volume phase transition temperature at around 40°C approaching that of the human body, and also due to the ability to reversible stimuli-responsiveness (60). Moreover, other approaches involved double-responsive composites, whose release was modulated by both pH and temperature (29,58,89).

One way of attaining better therapeutic outcomes and fewer problems of variable bioavailability is transdermal administration of low molecular weight and hydrophobic drugs. An adhesive developed for this purpose was pressure sensitive. The fabrication of a composite based on organomodified montmorillonite and polymethylsiloxane overcame an adhesiveness problem commonly observed in this system by using surfactant permeation promotors. In addition, loading of Solvent Blue 35 dye was improved by modifying the clay with an amine surfactant, because in this way there was better interaction between the polymeric matrix and the clay. While dye release decreased by 50% after a 10 day period in systems containing 2% organoclay and by 75% for samples containing 5% and 10% modified montmorillonite. Initial burst release of the loaded molecule was controlled and mechanical strength was optimized (33).

Besides the previously mentioned stimuli, release systems can also be responsive to electrical fields. However, most polymers cannot sustain this type of stimuli. Liu et al. (2008) prepared nanocomposites by adding montmorillonite to a chitosan matrix. This nanocomposite has good stability when submitted to electrical stimulus, unlike polymeric hydrogel, which suffers retraction with expulsion of water and drug when

electrostimulated. The increased ratio of montmorillonite altered the Vitamin B12 release mechanism of the chitosan hydrogel to the controlled diffusion mode because the high degree of crosslinking provided by the clay prevents swelling of the matrix. Formulations containing over 1% clay maintained release of drug at a constant rate during the course of repeated cycles of electrostimulation while deterioration of the polymeric matrix with repeated stimuli modifies the release rate. Differently the hydrogel without clay is protonated with H^+ originating from the electrolysis of water, resulting in repulsion between the chitosan chains and ultimately syneresis. The result obtained indicates that the nanohydrogel is a suitable platform for pulsatile drug delivery (38).

In recent years, there has been a rise in the number of publications focused on modified drug release, highlighting the importance of simplifying therapy to improve patient adherence. To this end, the active substance should be concentrated at the target site, minimizing undesirable systemic effects, or the frequency of administration reduced (96). Residence time of the clays in the body is dependent not only on their properties, but mainly on the biodegradability and stability of the polymer reinforced by the clay in biological environment. Interactions between the polymeric matrix and the clay generate a composite with distinct physicochemical properties such as mechanical strength, swelling ability, responsiveness of the pristine materials, which directly reflects on the release kinetics of the drug from this system.

The modified release systems promote changes in the rate, onset or site of release of the active ingredient and are named accordingly. Among the parameters cited, the last two are the most readily changed in a formulation. Several of the release systems based on the composites analyzed in the articles reviewed are given in Table 3.

Sustained release of paclitaxel nanoparticles based on poly(D,L-lactide-co-glycolide) (PLGA) and montmorillonite led to increased drug retention time due to the interaction between the nanoparticles and the mucus/epithelium of the gastrointestinal tract. The composites containing 25% (NP1) and 37% (NP2) clay increased the retention efficiency of nanoparticles by Caco-2 (57-177%) and HT-29 cells (11-55%), when compared to PLGA nanoparticles. This modification results in greater bioavailability because the anti-cancer drug has a greater first pass effect and their incorporation into nanoparticles avoids P-glycoprotein recognition in enterocytes. Initial release is slightly reduced from 22% in PLGA nanoparticles to 20% in NP1 and 18% in NP2 (31). The antihypertensive atenolol also has low oral absorption and short half-life, which results in limited bioavailability. Preparation of PLGA/ montmorillonite nanoparticles also extended gastric retention time of atenolol, reducing the initial rapid release characteristic of the systems obtained with this polymer. Because the addition of clay increases the stability of PLGA in acid, as well as the intercalation of the drug offers a more tortuous pathway for its release (32).

In addition, the gastro-resistance effect of some formulations can have utility when intended to protect the drug from prior degradation in acid media, safeguarding the patient against the irritant action of the drug in the stomach or optimizing intestinal absorption. Hydrotalcite microparticles with Eudragit® L100 (soluble at pH>6) and S100 (soluble at pH>7), reduced rapid dissolution of sodium diclofenac in the stomach environment, in order to obtain the colonic release of this anti-inflammatory drug.

Table 3. Modified drug release systems based on polymer-clay composites.

Composite	Drug	Site of release	Release system	References
Carboxymethyl cellulose/Vermiculite	Chlorhexidine	Oral mucosa	Controlled	(74)
Chitosan/Montmorillonite	Vitamin B12	Gastrointestinal tract	Pulsatile	(38)
PLGA/Montmorillonite	Paclitaxel; Atenolol	Stomach	Sustained	(31,32)
PLGA/Halloysite	Tetracycline hydrochloride	Intestine	Prolonged	(69)
Polyurethane/Montmorillonite	Triamcinolone acetonide	Intestine	Sustained	(21)
Derivative of acrylic acid/Layered double hydroxides	Diclofenac	Colon	Retarded	(68)
Chitosan/Montmorillonite	Diclofenac	Colon	Controlled	(37)
Starch-graft-poly(methacrylic acid)/Montmorillonite	None	Vagina	Controlled	(45)

The composites remained intact at pH 1.2 for 2 hours, attaining maximum release only at an alkaline pH. Microparticles containing hydrotalcite/Eudragit L ratio 1: 5 and 1:10 released 35% and 26%, respectively, after 90 minutes at pH 6.8. Samples prepared with Eudragit S in proportions 1:5 and 1:10 (relative to the polymer) reached 70% after 6 hours and 70% after 8 hours, respectively, at pH 7.5. The release mechanism of diclofenac in basic pH is attributed to the ion exchange of the drug by phosphate ions present in the dissolution medium, as well as to the anionic nature of the copolymers. The data were better fitted to the Baskar's equation, although Higuchi model was also adequate confirming that drug diffusion limits the rate of dissolution (68).

The objective of the study of Dagnon et al. (2009) was to overcome the low solubility of the active ingredient ibuprofen by incorporating it into a poly(L-lactic acid)/layered double hydroxide composite. Composites showed fast initial release (the first 15 hours), followed by a slower release for up to 50 hours, possibly due to the diffusion of ibuprofen adsorbed on the surface of the lamellar double hydroxide, that provided a short pathway for drug diffusion. Modified Freundich model was better fitted to the release of ibuprofen, which was characterized by diffusion controlled mechanism. Increase in the percentage cumulative drug release was proportional to the concentration of layered double hydroxide in the composite (63). This result mirrors those of Deleon et al. (2012) that assessed a similar system in which ibuprofen release during the first few hours occurred due to desorption of the drug onto the surface of the composite, followed by slow release due to the ion exchange mechanism, a characteristic inherent to some clays (64).

Martin et al. (2011) and Campbell, Craig & Macnally (2010) produced sustained and retarded release hybrid systems for ibuprofen, respectively. Polyvinylpyrrolidone and organoclay nanocomposite released 80% of the ibuprofen content in 10 days, while organoclay completely released the drug after one day. (67). Compounds of poly-ε-caprolactone/fluoromic and poly-ε-caprolactone/montmorillonite increased the release time of 25% and 50% of ibuprofen by 230% and 133%, respectively, when compared to the polymeric system. Release kinetics studies indicate that the composites exhibit Fickian behavior, and the most rapid diffusion was related to the drug dispersed in the pristine polymer (41). The shift in the release profile of ibuprofen can be attributed to the greater density of the polymeric matrix in the presence of clay and to restricted diffusion path by incorporation of the drug within the sheets or pores of the clay (67,97). In addition, the acidic drug has more affinity for the organoclays, resulting in a delay in its release.

Modified release was also observed in antibiotic and chemotherapeutic agents. Sustained release of tetracycline was achieved by PLGA and halloysite nanofibers. Incorporation of the drug into the nanotube followed by dispersion in a polymeric solution reduced the intensity of initial release and promoted slow release of the antibiotic over the course of 15-28 days (69). The chemotherapeutic agent doxorubicin was encapsulated in unilamellar vesicles comprising PLGA and organophilized laponite, with the addition of Pluronic F68 using the double emulsification method. The system exhibited good cellular permeability and biocompatibility, maintaining release of the active ingredient for four days (57).

Technological Prospection

After retrieval of the published articles, a search was conducted of patents related to the topic. The number of documents retrieved fell with increased refinement of the search criteria, as illustrated in Table 4. The highest numbers of patents were found at the World International Patent Office, likely due to the larger number of affiliated countries. No patents on the subject were found on the INPI. This finding indicates that Brazil, although boasting clay reserves with economic potential, has not yet sought to commercially exploit the composites derived from this material.

Restricting the search to include only composites involving clay and polymeric materials led to a marked reduction in the number of patents found, indicating the use of other elements to generate hybrids, such as metallic particles. The results also showed that the use of these composites as drug carriers represents only a small percentage of the lodged patents retrieved using the A61K international classification code as the search term. This confirms that patents of composites for pharmaceutical applications do not represent a significant proportion relative to other areas, such as electronic, petrochemical and environmental fields.

Among the patents classified by the A61K code, there was a high number related to the development of hydrogels as drug carriers or medical devices, which was also one of the most reported systems by the articles selected. The polyvinyl alcohol and montmorillonite hydrogel was patented for controlled gentamycin release in document US20130224256 (98).

Table 4. Number of patent requests for clay-polymer composites lodged by database.

Descriptors	inpi	uspto	EpO	WIPO
Composite or Nanocomposite	985	60,920	> 10,000	455,861
Composite or Nanocomposite and Polymer and Clay	5	120	970	943
Composite or Nanocomposite and Polymer and Clay (A61K)	0	2	22	22

This system is similar to that reported in one of the articles analyzed (49), which described the release mechanism of gentamycin based on a composite of these materials.

The patent WO2012104867 addressed a route seldom employed for applying composites, namely, the ophthalmic route. This patent pertains to the development of an ophthalmic gel for corneal repair based on monomers of hydrophillic polymers (acrylamides and methacrylamide) and delaminated clays of the smectite class (montmorillonite, saponite, hectorite and mica) that are chemically reticulated. This transparent, safe, sterile composite with high optical transmission, enables repair of the cornea without the need for transplant by fixation of corneal endothelial cells (99).

Patent US20040213846 relates to extended drug release based on nanocomposites. The composition of the hybrids involves polymers prepared by polymerization of unsaturated ethylene monomers derived from acrylate, whose choice depends on the intended application. The clay forming this nanocomposite must be susceptible to exfoliation, such as hydrated aluminium silicates, preferably montmorillonite. According to the authors, this system is suitable for release of antibiotic, anti-cancer, anti-parasitic, anti-inflammatory and anti-histaminic agents, as well as hormones, vitamins and drugs for diseases of the Central Nervous, Cardiovascular and Gastrointestinal Systems. The active ingredient entrapped within the nanocomposite is released by dissolution, swelling, or both (100).

The patents US09192625 (101) and RU0002424797 (102) suggest improvement of antimicrobial activity of the composites by introducing clay to the polymeric matrix as a strengthening material. In the first patent, hybrid films and fiber materials promote prolonged drug release and enhance mechanical properties. The composites of nylon and clay modified with quaternary ammonium salt and copper proved effective against *Staphylococcus aureus* and *Escherichia coli*. In patent RU0002424797, layered clay is modified by a guanidine derivative and a quaternary ammonium salt susceptible to polymerization. Organophilized clay is then added to the synthetic percha, a subproduct of latex applied in dental material.

Pavithran and Nair (103) patented microcapsules under US 2012/0225127 A1, developed by *in situ* polymerization of vinyl monomer in a smectite type clay modified with polysilsesquioxane. This spontaneously-formed nanocomposite can encapsulate drugs in just a few steps. The use of the *in situ* polymerization technique frequently cited in the articles also occurs in the processes described in patents for to get more finely dispersed composites.

The content of these patents was consistent with the results of the search of scientific output carried out during the same period, whereby montmorillonite was the clay of choice, while acrylates featured as the most commonly employed polymeric matrix. The drugs loaded in these systems are more diverse, since the benefits of controlled release based on hybrid systems are widely recognized. Some of the patents were lodged with more than one office. The country with the highest number of patents was Japan, whose intellectual property of composites was requested mainly by companies manufacturing healthcare-related products. Patent requests were lodged from the late 1980s, with declining intellectual protection over ensuing years, as shown in Figure 9.

In view of the number of publications, it is evident that researchers have sought solutions for drug release systems by developing clay-polymer composites for the benefits previously outlined. However, the intellectual property related to this area remains very low, despite being processes and products with high market potential.

One hypothesis for this low number centers on the regulatory gap regarding these novel materials, in addition to lack of knowledge on their efficacy and safety profile. Besides the great potential of organic-inorganic combinations, data from toxicological studies are highly conflicting and pertain mostly to *in vitro* models (104). These results indicate that further studies with a technological emphasis should be carried out in this segment, since no correlation exists between the volume of articles published and number of patents lodged.

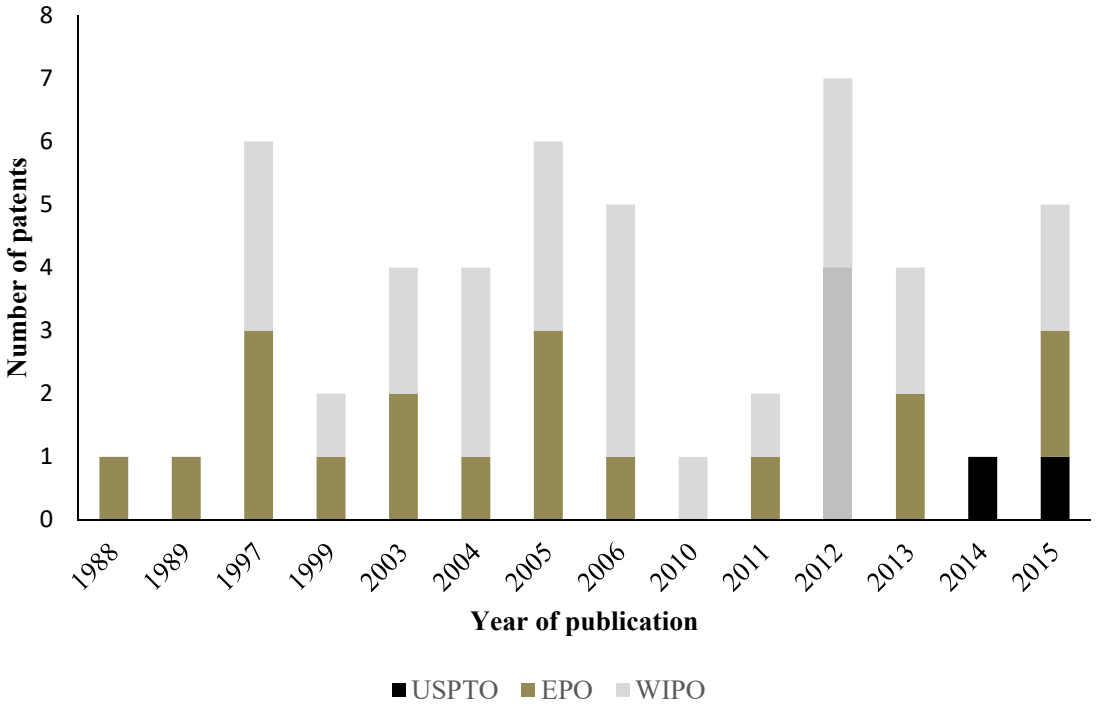

Figure 9. Distribution of patents retrieved pertaining to subclass A61K, by year of publication.

CONCLUSION

Based on this prospection, it can be concluded that numerous composites have been synthesized and characterized with promising benefits as drug carriers, for example greater mechanical resistance and thermal stability as well as modulation of the release of bioactive molecules through chemical and physical stimuli. Articles are commonly constrained to anti-inflammatory, antimicrobial and chemotherapeutic drugs, which in many cases require controlled release to avoid dose dumping and consequently minimize adverse effects, or to improve the bioavailability of drugs with regards to their half-life or low solubility. However, these systems could be applied to drugs for neurological, hormonal and metabolic disorders, or other conditions requiring controlled rate of release and are related to chronic treatments. Most composites involved modified clays, especially montmorillonite, in order to achieve a better compatibility with organic matrices. This clay is recognized for its high ion exchange capacity and approved for pharmaceutical use by agencies in several countries. Composites derived from the association of clays with natural and synthetic polymers have good compatibility in *in vitro* studies. Some studies in vivo have been carried out in order to elucidate the influence of their reduced size on distribution and interactions in biological environment. The absence of regulation on nanomaterials used in the development of medications has likely stymied commercial interest in these potential carriers. This may explain the low number of patents related to composites employed in therapeutic devices. However, examples of effective and safe composites encourage the application of these systems in the production of medicines.

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