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Clays as Biomaterials in Controlled Drug Release: A Scientific and Technological Short Review

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Abbreviations: EPO: European Patent Office; USPTO: United States Patent and Trademark Office INPI: National Institute of Industrial Property; APTES: Amino-Propyl-Tri-Ethoxy-Silane

ABSTRACT

The use of clays as vehicle for drug release has been investigated in the scientific environment. This work aims to review articles and patents that present the use of clays in formulations to carry and release drugs. The Scopus, Scielo and Web of Science data bases were used to search for articles and the European Patent Office, United States Patent and Trademark Office and National Institute of Property databases. According to the exclusion criteria, the only articles used were the ones that had the combination of keywords (clays and drug release). The clays studied were used in their natural, synthetic or modified form. The parameters that influence the release of the drugs also were: effect of PH, effect of clay quantity and kinetic study. In view of the excellent performance against the controlled release of drugs, it is evident that there is growing interest in the scientific-technological field in the use of different clays as inorganic support for adsorption and desorption in pharmaceutical compositions.

Keywords: Clays; Biomaterials; Controlled Release of Drugs

Introduction

For many years research has focused on the development of new carriers for controlled release of drugs. Among numerous nanoscale substrates used for drug delivery, special attention has recently been given to clays because of their chemical and morphological properties. Clay and clay minerals with their different structures, such as lamellar, fibrous or tubular, are the main choice for the design of biomaterials due to its low cost, important intercalation chemistry and low toxicity, allowing them to be chemically modified to improve compatibility with organic molecules [1–3]. The various fields that encompass the applications of clays are mainly in civil engineering, paper industry, effluent treatment, photocatalysis, tissue engineering, cosmetics, controlled drug release and others. These materials can be used in manipulations for drug encapsulation both for dermatological application and for oral administration, thus being important material to be exploited in various technological processes, specifically in the pharmaceutical industry [2,4-15]. The objective of this works a bibliographical and technological prospection regarding clays and clay minerals, including their characteristics and modifications, with emphasis on their use as biomaterials, controlled release of drugs.

Materials and Methods

The research was done in the period of 2007-2018, using the Scopus, Scielo and Web of Science databases; and patent databases: European Patent Office (EPO), United States Patent and Trademark Office (USPTO) and National Institute of Industrial Property (INPI), Brazil. The search was performed according to the combined keywords: Clay, phyllosilicate, functionalized, organophilic, organomodified, synthesis, organofunctionalization and "drug

delivery system". For the review of articles, we analyzed the journal base with the keywords and combinations "article, title, abstract and keyword", "all indexes" and "topic", respectively. Review articles and chapters of books were not included in the survey, in addition to papers published in the year 2019. Due to the diversity of articles found, some exclusion criteria were used to restrict the search in order to limit it to articles used, with natural or synthetic cationic clays in controlled release of drugs.

Results and Discussions

Published Articles

The use of the more generalized expressions such as Clay, "Drug delivery system" and Phyllosilicates, showed a greater amount of publications. However, combinations of the expressions, denote a refinement in there search about the analyzed subject, causing hat a smaller number of publications is displayed Table 1 shows the numbers of publications found in the databases cited above. When analyzing (Table 1) it is verified that the Scopus database is the one with the largest number of published articles, while Scielo presents a limitation of publications, even for the most generic expressions. Of the total of 81 articles, it was noticed that some articles are repeated. Based on the exclusion criteria, a brief classification of the profile of the articles and their different objectives could be carried out, which were divided according to the applications. In this study, there presentation of articles indicates that modified or unmodified clays, and combinations with different drugs have majority function in the survey. According to the study of the annual evolution of publications, the use of clays as biomaterials for controlled drug release has been investigated significantly in the last ten years, being the year 2016 the most representative in this segment. (Table 2) presents the main articles and their peculiarities in the different systems (clay AND drug) used for the purpose of incorporating and releasing the drug in the human organism. Among the evaluated drugs, the classes are: analgesics [4], anticancer [16-18] antibiotics, anti-inflammatories [19,20] antibacterials [20-22] and vitamins [23-25]. The clays, natural or synthetic, that stand out in these studies are: montmorillonite, halloysite, laponite, palygorskite and magnesium phyllosilicates. Among the phyillosilicate classification, montmorillonite is prominent within the biomaterials area, because it presents excellent intercalation properties, adsorption capacity and cation exchange, water dispersibility, high surface area, swelling capacity and optimum rheological behavior, as well as its properties. abundance in nature and low cost [4,18,26-32].

Table 1: Number of articles found in the Scopus, Scielo and Web of Science database.

Keywords	Scopus	Scielo	Web of Science
Clay	77.075	2.078	74.387
"Drug delivery system"	67.749	51	11.756
Phyllosilicates	1.182	13	1.368
(Clay OR phyllosilicate) AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis)	4.377	90	4.871
Phyllosilicate AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis)	123	0	132
(Clay OR phyllosilicate) AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis) AND "Drug delivery system"	45	0	30
Phyllosilicate AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis) AND "Drug delivery system"	3	0	3

Table 2: Types of clays and drugs in the analyzed articles.

Clay	Drug	Reference
Montmorillonite	Tetracycline hydrochloride	[16]
Montmorillonite	Doxorubicin	[17]
Montmorillonite	Paracetamol	[4,18]
Montmorillonite	Diltiazem hydrochloride	[19]
Montmorillonite	Ibuprofen	[20]
Montmorillonite	Methyldopa and theophylline	[21]
Montmorillonite	Docetaxel	[22]
Montmorillonite	Pomegranate	[23]
Montmorillonite	Vitamin B1	[24]
Montmorillonite	Venlafaxine Hydrochloride	[25]
Montmorillonite	Vitamins B1 and B6	[26]
Montmorillonite	Chlorhexidine acetate	[27]
Montmorillonite	Doxycycline	[28]

Montmorillonite	Propranolol Hydrochloride	[29]
Montmorillonite	Clopidogrel bisulfate	[1]
Montmorillonite	Naproxen	[30]
Caulinite, halloysite, montmorillonite	Epirubicin, fludarabine, gemcitabine	[31,32]
Halloysite	Doxycycline	[33]
Halloysite	Diphenhydramine hydrochloride	[34]
Halloysite	Curcumin	[35]
Halloysite	Diphenhydramine hydrochloride	[36]
Halloysite	Silibinin and curcumin	[37]
Cloisite	Sodium diclofenac	[38]
Palygorskite	Sodium diclofenac	[39]
magnesium phyllosilicates (talc)	Flurbiprofen	[40]
magnesium phyllosilicates	Pelubiprofen	[41]
Laponite	Doxorubicin	[42]
Hectorite (Laponite)	Sinomenina hydrochloride	[43]

Halloysite, an aluminosilicate with a tubular structure, compared to other nanoparticles such as carbon nanotubes, is a type of natural inorganic tube, cheap, abundantly available, eco and biocompatible [33], because of this has much application for drug releases [34-36]. Laponite, a synthetic hectorite, has specific properties, such as high purity, excellent cation exchange capacity and mechanical toughness, tensile strengths, good extensibility, high transparency, low cost and easy processing [37]. Palygorskite is the most commonly reported fibrous clay in the literature [38-40] and presents great potential for retention of pollutants, drilling fluids, adsorption and in the pharmaceutical industry [41,42]. Magnesium phyllosilicates of talc type are compounds that present the possibility of modification of their inorganic structure and the viability of insertion of molecules in their lamellae, during the functionalization of the material [43].

Articles Research

Synthesis, Treatments and Modifications of Clays: Physical or chemical changes in the structure of clays are of great industrial interest, generating new materials with specific properties which allows to extend their applications [44]. In this sense, lamellar or fibrous clays can be modified with various organic compounds, giving rise to hybrid materials commonly known as organoclays [4]. The organofunctionalization is one of the most reported modifications in the literature for the application of clays as nanocomposites [16,45,46]. This research has been highlighted due to the improvement of thermal, mechanical and rheological properties, among others [47].

In the case of montmorillonite, a variety of systems are involved in the release of drug, either in the natural form synthetic [48-51] or modified [30,46,52-55]. In one of these works synthesized montmorillonite by the hydrothermal method and employed in drug delivery systems [4] made use of acid activation to treat natural montmorillonite [34] used two distinct steps to synthesize a polymer / clay hybrid material; in the first step modification of the natural halloysite was achieved by incorporation of the drug (diphenhydramine hydrochloride) and thereafter the second step was continued by the addition of polymer (polyvinyl alcohol), with the aim of reducing the rate of drug release. In the research by [56,57], halloysite nanotubes were functionalized with 3-aminopropyltriethoxysilane (APTES) from hydroxyl groups by a coupling reaction. Dental adhesives were developed in the work of [33] using natural halloysite nanotubes as an inorganic support for the encapsulation of the drug doxycycline. Hydrogels composed of polymers (chitosan and polyvinyl alcohol) were developed by [52], this paper evaluated the influence of the percentage of laponite in the hydrogels, noting the presence of the clays. [58], developed a dendrimer, in the form of nanodiscs, using laponite in its structure. The clay was silanized and modified with succinic anhydride to yield abundant carboxylic groups on its surface and finally conjugated with dendrimers for further incorporation of the drug under study.

The hectorite was applied in the studies of [59] to synthesize different printed molecular polymers, varying the amount of hectorite present. Compound microspheres have been described by [60] this system was based on hybridization of chitosan and palygorskite organo-modified, prepared by emulsion cross-linking technique and applied as drug carriers. Palygorskite was modified with hexadecylbetaine (BS-16) to improve compatibility and affinity with the chitosan matrix, enhancing the encapsulation and migration of the drug.

Parameters that Influence Controlled Release: Many drugs are insoluble in aqueous media and / or biological fluids and therefore their effects are decreased due to the low bioavailability. To improve their solubility, the drug molecules can be incorporated into the interlamellar space of pure or modified clays, generating a biomaterial. This pharmaceutical form enables the uniform release of drugs in the body, maintains the therapeutic level with low oscillation, prevents toxic levels and local and systemic side effects [61]. The interaction between the components of the biomaterial

formulation (drug, clay and other constituents) will determine the way and the rate with the drug is released from the matrix. Some parameters directly influence the controlled release process, such as the effect of solubility,effect of PH [62,63], effect of clay quantity drug effect carried and kinetic study [4,45,58].

Effects: PH, Amount of Clay and Kinetic Release Study

Anirudhan and the collaborators [18] analyzed the cumulative release percentage in means 1.4 and 7.4. The results indicated that increasing the P^H from 1.4 to 7.4 shows a considerable increase in cumulative release. It was observed that 85.0% of paracetamol was released in 10 h at P^H 7.4, while only 64.0% was released at P^H 1.4. This suggests that the drug release properties are p^Hsensitive. In the study by [63] the percentages of release decrease with increasing P^H from 4.0 to 6.5, due to a possible change in the release mechanism during the process. According to the authors the mechanism of dissolution is the main responsible for the behavior of release of the drug at P^H 4.0, while the ion exchange is responsible at P^H to 6.5. [4] evaluated different percentages of clay (0, 2, 10 and 20%). There was a decrease in the rate of drug release with an increase in montmorillonite. Since the mechanism of drug release from hydrogel results from both drug diffusion and swelling of the hydrogel. For the authors [4,20,46] all results suggest that it is possible to prepare nanocomposites in which their properties can be controlled by the clay content present in the nanocomposite. Numerous studies are reported in the literature regarding the kinetic release study profile [18-20,59-61]. In the studies ofthe kinetics of *in vitro* release of 10-hydroxycamptotcin from the nanocomposites were adjusted to the kinetic model of pseudo-second order. The kinetics of doxycycline drug release investigated by [64], inserted in the nanocomposite composed of chitosan, cloisite and polycaprolactone, the values of k and n were calculated, indicating a change in the release. In the studies of [39], in a microspheres system composed of palygorskite and diclofenac sodium, the drug release process was better adjusted to the Ritger-Peppas model.

Patents Research: The results of the survey carried out in the EPO (European Patent Office), USPTO (United States Patent and Trade Mark Office's) and INPI (National Institute of Industrial Property) are presented in Table 3. The review was carried out with the pre-defined keywords - defined and mentioned in the study of articles. According to the patent results, only one of these meets the main idea of this prospecting and literature review, according to the limited keywords. The patent (US 20090232887 A1) aims to provide a pharmaceutical composition that effectively assists the control in the release of the active substances, such as tramadol and oxycodone (analgesics). It discloses the use of clays (bentonite) in the synthesis of a pharmaceutical slurry, representing about 1.0-2.5% by weight of the composition containing both dicarbomer and hydroxypropyl methylcellulose, active in the matrix for controlled release [65-68].

Table 3: Quantity of patents deposited in the EPO, USPTO and INPI databases without time interval.

Keywords	EPO	USPTO	INPI
Clay	>10.000	5.631	263
"Drug delivery system"	7.770	870	2
Phyllosilicate	1.471	192	7
(Clay OR phyllosilicate) AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis)	1.305	1276	-
Phyllosilicate AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis)	32	103	0
(Clay OR phyllosilicate) AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis) AND "Drug delivery system"	0	3	-
Phyllosilicate AND (functionalized OR organophilic OR organomodified OR organofunctionalization OR synthesis) AND "Drug delivery system"	0	0	0

Conclusion

The data presented in this prospection confirm the growing and current interest of the researchers in obtaining hybrid materials with potential for application in controlled release of drugs, a fact evidenced by the number of publications that use different clays and clay minerals as a vehicle for transportation and release in pharmaceutical systems. The analysis of these publications shows the variety of systems used for release, as well as different syntheses and modifications of the clays to improve their properties, as well as parameters that influence the release process such as time, temperature, dosage, P^H, system composition, solubility drug, and others. These parameters are shown as an important tool in elucidating the possible interactions between clay/drug and the biological environment, helping to clarify how the process of release of the materials under study can occur. In view of the expressive scientific results discussed herein, clays can be considered for the formulation of pharmaceutical excipients as drug carriers.

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