Tuberculosis: the use of clay minerals nanoparticles to leverage isoniazid treatment efficiency, a promising future

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1 INTRODUCTION

Tuberculosis is a globally widespread infectious disease with elevated transmissibility and expressive mortality rate. It affects people throughout all age groups causing a strong economic impact on public health systems. Isoniazid, which was launched in the market in the 60's, has been the most effective antimicrobial drug for the treatment of tuberculosis so far. However, this is a long treatment with many adverse effects resulting in poor patient compliance. Therefore, it is necessary to develop oral intake systems that minimize the adverse effects of the drug to guarantee patients adherence to the treatment. Over the last decade, extensive research has shown that the development of controlled release systems is an effective way of addressing isoniazid's adverse effects. The intercalation of isoniazid in clay minerals such as bentonites present highly promising results and accounts for one of the uttermost contributions of material engineering science to human medicine. The present study review seeks to summarize and allow readers to understand the most recent researches on this subject.

2 TUBERCULOSIS AND TREATMENT CHALLENGES

Tuberculosis is a serious public health problem with a high prevalence in developing countries. The agent for human tuberculosis is the bacterium *Mycobacterium tuberculosis.* According to the WHO (Word Health Organization), in 2018 about 11 million new cases of human tuberculosis were reported, of which 1,6 million resulted in

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deaths. In addition, health authorities estimate that tuberculosis cases may significantly increase, since its treatment may be neglected, due to the pandemic of Covid-19 (WHO, 2020).

The main transmission mechanism of *Micobacterium tuberculosis* is aerogenous, being exhaled with the patient's breath and may potentially infect people in a radius as far as 12 meters. Depending on the immunity conditions, individuals exposed to the bacillus may develop the active or the latent form of tuberculosis. The former is the classic one with clinical signs, and the latter occurs when the immune system can contain the proliferation of the bacteria without any apparent clinical signs. However, this can evolve into an active form within two years or more, making this individual a new source of transmission to other people (DUARTE et al., 2010).

It is important to point out that tuberculosis is a bacterial zoonosis: it infects not only humans but also other mammal species, with special importance given to cattle, which are infected by a bacillus variant called *Micobacterium bovis*. In addition, both bacteria, *M. tuberculosis* and *M. bovis* can indistinctly infect humans and other mammals. The main form of transmission of *M. bovis* to humans is the consumption of unpasteurized milk and raw or undercooked meat. In Brazil, the treatment of tuberculosis in cattle is not allowed, being compulsory the sanitary slaughter and proper disposal of the carcass. Therefore, the control of tuberculosis is of extremely importance not only from a public health perspective but also due to its strong economic impacts (MURRAY; MENDEL; SPIGELMAN, 2016; WILSON et al., 2020).

Despite being a serious disease, tuberculosis is curable in more than 90% of the cases, provided there is a complete adherence to the chemotherapy and the protocol is strictly followed by patients. Within four to six weeks of treatment the patient experiences a considerable improvement in clinical symptoms (also known as a sensation of clinical cure) and even stops transmitting the bacillus in the form of a respiratory aerosol. Whereas the full course of treatment in general takes from nine to twenty-four months to achieve the effective cure (ALLAND et al., 1998; OROFINO et al., 2012).

The drug of first choice for treatment of tuberculosis is the antimicrobial isoniazid, which is a hydrazide derived from isonicotinic acid and operating primarily like a bactericidal agent. The route of administration of isoniazid is oral although it can be

intramuscular or even intravenous in critically ill patients, being absorbed and diffused quickly into corporal fluids and tissues. The therapeutic dosage recommended for isoniazid is 5-10 mg/kg of the patient's weight till the limit of 300 mg/day. Bioavailability of this drug is approximately 30% to 40% and first-pass metabolites are responsible for the adverse effects of the treatment, with emphasis on hepatotoxicity which requires constant clinical and laboratory monitoring of the patient (OROFINO et al., 2012; WYSZOGRODZKA-GAWEŁ et al., 2019).

Adverse effects such as skin reactions of hypersensitivity, peripheral neuropathy, seizures, headaches, among other side effects may be present all over the treatment. It is not uncommon for the patient to develop drug induced hepatitis. The treatment protocol of tuberculosis may also include the combination of isoniazid with other drugs, depending on the patient's clinical situation (WYSZOGRODZKA-GAWEŁ et al., 2019).

Micobacterium tuberculosis or *Micobacterium bovis* are classified as mycobacteria and are slow growing microorganisms whose cell walls are protected by lipids. The cell walls provide the bacteria a considerable degree of impermeability to several antimicrobial agents and even develop the ability to select specific resistant strains for a particular drug. Therefore, it is required to establish appropriate treatment strategies to address these intrinsic characteristics of these bacteria. It is a general knowledge in microbiology science that antimicrobials are more effective in the treatment of diseases originated by fast growing microorganisms, which is not the case of tuberculosis. Treatment of diseases based on slow growth mycobacteria take longer periods, months, or years, at determined plasmatic concentrations to achieve the effective cure of the patient (GE et al., 2018; KATZUNG, 2006).

One of the biggest challenges in the treatment of tuberculosis is the abandonment of the therapy by patients because of the side effects and the elevated number of pills taken daily at fixed times. This poor patient compliance is one of the main factors responsible for the selection of bacteria strains that are resistant to isoniazid. According to WHO in 2017, approximately half a million new cases of tuberculosis resistant to isoniazid were reported and had to be treated with different combinations of antimicrobials, but nevertheless they resulted in more than 250.000 deaths. Because of that, it is necessary to develop strategies that might reduce the frequency of drug

administration to patients, allowing better patient compliance (ALLAND et al., 1998; SCHUTZ et al., 2020).

The drug with predominant use in tuberculosis treatment is isoniazid, a synthetic derivative of isonicotinic acid, water soluble and has a molecular weight of 137 g/mol, approximately. It is the most active drug in treatment of all forms of tuberculosis, except in case of drug resistance. It is a low-cost drug and was introduced in the market back in the 60's and a consistent basis of information on its clinical use has been accumulated throughout these years. Isoniazid action mechanism is being a pro-drug that activates bacteria peroxidase catalase enzyme system inhibiting the synthesis of mycolic acid, which is responsible for the stiffness of the cell wall, and allows permeation of the drug (CARRIER, 1999; RODRIGUES; SHENDE, 2020).

In vitro controls demonstrate that a concentration of isoniazid of 0,2 µg/mL of blood is effective against the growth of tuberculosis bacillus (NKANGA; KRAUSE, 2019).

Regarding adverse effects of tuberculosis treatment, the incidence and severity of might vary with doses administered as well as time of administration. Despite disappearing completely at the end of treatment, febrile episodes and skin rashes are commonly reported, including the development of drug-induced systemic lupus erythematosus. These side effects that may affect many patients are related to isoniazid allergic processes in the body of sensitive individuals. Another negative aspect of the treatment of tuberculosis is the high number of pills taken daily at fixed times, in order to keep a constant plasmatic concentration of the drug (AMARNATH PRAPHAKAR et al., 2017; ZHANG et al., 2014).

Toxicity symptoms caused by treatment with isoniazid are far worse than the reported side effects above and frequently induce patients to grave consequences. Symptoms like anorexia, nausea, emesis, jaundice, and pain in the right hypochondrium, which in combination may be fatal if treatment is not interrupted immediately. This collection of symptoms is an indication of liver function failure and should not be misunderstood as derived from aminotransferase enzymes increase. The increase of these enzymes, sometimes up to three or four times above normal levels, happens in approximately 20% of the population treated with isoniazid, although some patients

remain asymptomatic, and after finishing the treatment it returns to normal levels, indicating normal liver function (NKANGA; KRAUSE, 2019).

Once isoniazid is orally ingested it will be absorbed in the upper gastrointestinal tract and be immediately transported through the hepatic portal system to the liver, where approximately 70% of it will be metabolized by the first-pass mechanism and inactivated before reaching the systemic blood circulation. This mechanism is dependent on the acetylation enzymes, especially N-acetyltransferases produced in the liver, which reacts with isoniazid transforming it into acetyl-isoniazid, a metabolite without curative properties and potentially toxic to patients. This mechanism is also known as premature isoniazid metabolism and is responsible for reducing the plasma concentration of the drug and may differ significantly among individuals. It is well recognized that fast acetylators individuals reach lower bioavailability than slow acetylators. However, according to recent studies, slow acetylators have greater tendency to hepatotoxicity (AMARNATH PRAPHAKAR et al., 2017).

Considering that INH is the most cost-effective drug for the treatment of tuberculosis, all efforts must be towards preserving its clinical effectiveness, which is being threatened by the emergence of resistance bacteria strains (BIZERRA; SILVA, 2016).

Resistance bacteria strains mechanism is based on clinical studies in volunteer patients with an average capacity for absorption, distribution, and elimination of the drug. However, it is not possible to maintain a standard dose for all patients, because the individual clinical condition must be considered. In general, relevant individual aspects are the degree of nutrition, maturity of physiological processes, preexistence of other pathologies such as renal and renal failures, among others. All these factors presented affect the pharmacokinetic parameters of a drug administered to a patient. In general, two parameters have great importance regarding planning a drug therapy: the pharmacokinetics and the pharmacodynamics. The first, pharmacokinetics, deals with the necessary drug amount to be administered to the patient, via a specific route, to achieve a determined plasma concentration of it. On the other hand, pharmacodynamics, is related to the minimum drug plasma concentration to obtain the necessary curative effect. Plasma concentration is the link between pharmacokinetic and pharmacodynamic processes and

is mainly represented by the binding of the drug to blood proteins, in 90% of cases, albumin (DE ALMEIDA et al., 2019).

Controlled release systems have as their main objective the stabilization of drug plasma concentration, using a carrier vehicle that continuously releases the drug at pre-determined rates to bind blood to plasma proteins. As an additional advantage, it allows the less frequent administration of doses and a smaller number of pills to be ingested by patients daily (DAMASCENO JUNIOR et al., 2020a; ZYOUD et al., 2016).

The rate of oral drug absorption is determined by gastrointestinal processes and the solubility of the drug in stomach fluids, and significantly affects the first-pass mechanism and its deleterious consequences. These consequences can be minimized or even eliminated using controlled-release formulations. In this case the drug is not absorbed or modified by stomach fluids and will be released continuously directly in enterocyte cells of small intestines and join plasma proteins proceeding with the desired therapeutic effect. These controlled-release formulations are subject of several studies of pharmaceutical science and represent a feasible strategy for the rational use of existing drugs whose misuse has led to the development of microorganism's resistance, which is the case of isoniazid. As an additional advantage when using the strategy of controlled-release formulations it is possible to administer higher doses at once, preventing the patient from forgetting to swallow several pills a day to maintain the necessary plasma concentration of the drug, thus, treatment adherence is much better, leading to higher and faster cure rates and minimizing the development of resistant strains of the bacillus (PANDEY; YADAV; MISHRA, 2016).

The development of a controlled release system for isoniazid is highly desirable since it is a drug with fast absorption, short half-life, and high liver first pass transformation. In addition to the necessity of keeping a constant plasma concentration for the inhibition of bacteria growth (CHEN et al., 2019).

3 CLAY MINERALS CARRIERS

New treatment strategies are being researched with focus in developing carriers that allow the controlled release of isoniazid, targeting a single daily or even weekly administered dose to the patient. Some nanoparticulated polymeric systems are very

promising alternatives. However, at higher costs and in some cases, there is not enough information on the resulting metabolization of these materials. The option for studying clays as carriers and controlled release agents is since they are low cost and fully biocompatible materials, currently being one of the main lines of research. The multilayered spatial structure with well-defined interplanar distances and ionic interactions, make them potentially useful materials for the retention of organic molecules and later release at controlled rates (ANNABI-BERGAYA, 2008; BERGAYA; THENG; LAGALY, 2005).

Clay minerals are generally described as hydrated silicates with a layered structure possessing either tetrahedral or octahedral configurations linked through common oxygen atoms. Two main clay minerals are presently among the most researched for the purpose of intercalation of isoniazid, i.e., bentonite and halloysite (BERGAYA; THENG; LAGALY, 2005).

Bentonite is a clay mineral belonging to the family of smectites having a 2:1 structure, with two silica tetrahedral sheets and one aluminum octahedral sheet, and lamellar morphology. The halloysite clays contain mainly the clay mineral halloysite, which has a 1:1 structure, with one silica tetrahedral sheet and one aluminum octahedral sheet, and its morphology is in form of tubes. Both are micro-nanoparticles (montmorillonite with diameters in the micro scale and thickness in the nano scale, and halloysites with diameters in the nano scale and heights in the micro scale) with relative low cost and easily processed in most pharmaceutical plants, not demanding additional and costly unit operations. Halloysite, bentonite, palygorskite and sepiolite are also potential candidates as carrier systems since they are not metabolized into by products when going through gastric system (BERGAYA; THENG; LAGALY, 2005).

The principle and the advantage of using clay minerals as carriers for isoniazid is related to these minerals' ionic characteristic and layered structures that allow the intercalation of the antimicrobial in the inner spaces between the layers, or in the intern part pf the halloysite tubes, also mentioned in some literatures as the lumens of the mineral. When it is swallowed by the patient and in contact with intestinal enterocytes, the mineral will start releasing the drug directly in the blood stream and will avoid the first pass mechanism, which is the main responsible for the adverse effects of the drug,

while allowing a constant plasmatic concentration (HANG et al., 2019).

In case of using kaolin, additional benefits are being studied since it may result in systems that could possibly associate other drugs, for example DMSO (dimethyl sulfoxide), a well-recognized non-steroidal anti-inflammatory agent, which resulting system may have a synergistic effect enhancing the cure of tuberculosis (SOJKA et al., 2008).

Different methods of intercalation are applied by specific researchers with predominance of water dispersion techniques. The group of palygorskite-sepiolite phyllosilicates, besides being widely used in different industrial and environmental processes, were also studied by Akyuz et al, 2010, with the purpose to intercalate isoniazid. The preparation of the clay mineral intercalated with isoniazid compared two processes, aqueous solution, and solid-solid reactions. Aqueous solution is the predominant method described in most literature and takes advantage of the high solubility of INH in water. The preparation consists of dispersing palygorskite-sepiolite into water under mechanical homogenization, added to a prepared solution of INH, the outcome is filtered, centrifuged, oven dried and grinded. The alternative method also explored by these authors consists in a solid-solid homogenization of both clay mineral and isoniazid, in the presence of a small amount of water, making this method simpler and potentially attractive for future process scale-up. The key focus of this research is the evaluation of final product via FT-IR spectroscopy, demonstrating that INH molecules adsorbed are correlated with endocyclic nitrogen in addition to Si-OH groups over clay surface (AKYUZ; AKYUZ; AKALIN, 2010).

Carazo et al, 2018b, studied the intercalation of isoniazid in palygorskite using the method of aqueous dispersion, where fixed amounts of palygorskite were dispersed into pre-prepared INH water solutions with initial concentrations varying from 0,05 to 0,5 mol/L, also varying temperature and time. The purpose of the study was to determine the thermodynamic stability of the system under different conditions, on top of establishing the percentage of INH loaded into palygorskite. The characterization followed traditional methods as XRD, FT-IR, thermogravimetry. Conclusions regarding the interaction of INH molecules and palygorskite, resulting from FT-IR essays, are like that shown by Akyuz in 2010.

Damasceno et al, 2020, studied the interaction of palygorskite and isoniazid under different pH conditions. The aqueous dispersion method used was like other authors, being a solution of water and clay added with a solution of INH in water, then stirred, sedimented, filtered, centrifuged, dried, and disaggregated. The additional point of this study is the use of a HCl solution used to fix different pH values, ranging from pH 6 to pH 2. Final evaluation of the intercalated product was carried out by XRD, FT-IR, microscopy, and zeta potential. Corroborating research above mentioned from Akyuz 2010 and Carazo 2018, this author demonstrated the intercalation of INH into palygorskite layers, resulting in a product suitable for controlled release (DAMASCENO JUNIOR et al., 2020a).

Considering the importance of adequately addressing the use of controlled release systems, mainly those based on clay minerals, table 1 shows some of the most recognized papers released over the last years and recommended for further consults. Table 1 indicates the clay utilized, a brief of the intercalation methodology, in the column **"Incorp"** it is stated the amount of isoniazid intercalated, if controlled release essays are performed, they are indicated with Yes or Not in the column **'Contr. Rel.",** and finally the author.

Table 1: Some articles related to Isoniazid and clay minerals

CLAY	METHODOLOGY	INCORP.	CONTR. REL.	AUTHOR
Montmorillonite Saponite	Immersing the clays in aqueous solutions of isoniazid in sealed bottles.	Not measured	no	(AKYUZ; AKYUZ, 2008)
Montmorillonite	Ionic crosslinking of chitosan with sodium TPP plus isoniazid and montmorillonite, stirred and sonicated.	Avg 27% w/w	yes	(BANIK et al., 2012)
Montmorillonite	Chitosan, -montmorillonite solution, then the addition of isoniazid solution, mechanical stirring, precipitation and centrifuged	Avg 60% w/w	yes	(BANIK; RAMTEKE; MAJI, 2014)
Montmorillonite	Soy flour and montmorillonite crosslinked particles as carriers to isoniazid	Avg 55% w/w	yes	(BANIK et al., 2013)
Montmorillonite	Aqueous dispersion	20% w/w	No	(CARAZO et al., 2018c)
Montmorillonite	Crosslinked gelatin- montmorillonite nanoparticles	Avg 70% w/w	yes	(SARMAH et al., 2015)
Bentonite	Bentonite modified with environmentally free process with glycine for the adsorption of isoniazid	34 mg/g	No	(ÇALIŞKAN SALIHI; GÜNDÜZ; BAŞTUĞ, 2019)
Montmorillonite	Aqueous dispersion, swelled for 24 hours, sonicated, then centrifuged	90% w/w	yes	(SUGUNALAKSHMI et al., [s.d.])
Montmorillonite	Synthesis of a montmorillonite and poly(o-toluidine) nanocomposite as a carrier agent	Avg 72% w/w	Yes	(VERMA; RIAZ, 2018)
Sepiolite palygorskite	Adsorption of isoniazid onto sepiolite-palygorskite group of clays, aqueous dispersion method	Not measured	No	(AKYUZ; AKYUZ; AKALIN, 2010)
Hydrotalcites	Hydrotalcite and isoniazid nanocomposite	20% w/w	Yes	(ELENA et al., 2019)

	obtained by aqueous process and precipitation			
Halloysite	Aqueous solution of halloysite and isoniazid, centrifugation	20% w/w	No	(CARAZO et al., 2017)
Palygorskite	Water solution of palygorskite and isoniazid, mechanically stirred, centrifuged, and characterized	20% w/w	No	(CARAZO et al., 2018b)
Halloysite	Dispersion of halloysite powder in isoniazid aqueous solutions	Avg 40$ w/w	yes	(CARAZO et al., 2019)
Palygorskite	Aqueous dispersion of palygorskite and isoniazid	12,93 mgINH/g PAL	Yes	(DAMASCENO JUNIOR et al., 2020b)
Perlite	Aqueous solution of silica perlite, isoniazid, under variation of relevant parameters	Avg 41% w/w	Yes	(DE ALMEIDA et al., 2019)
Iron oxide CMC	Carboxymethil starch-chitosan-coated iron oxide magnetic nanoparticles, in aqueous solution process	Avg 23% w/w	Yes	(SAIKIA et al., 2015)
Montmorillonite	Nanoparticles obtained from montmorillonite combined with thiolated starch.	Avg 29% w/w	Yes	(SAIKIA et al., 2014)
Zeolites	Water dispersion of zeolites and isoniazid under specific conditions	Avg 60 mg/g	No	(SOUZA et al., 2020)
Faujasita	Aqueous dispersion of faujasite and isoniazid in controlled acid pH	Avg 25 mg/g	Yes	(SOUZA et al., 2021)

Accordingly, to the articles showed at the Table 1, MMT can be used as a carrier itself (AKYUZ; AKYUZ, 2008; CARAZO et al., 2018a; SALIHI; GÜNDÜZ; BAŞTUĞ, 2019; SUGUNALAKSHMI et al., 2014) or as a filler in a polymer matrix to obtained composites that will made micro or nanoparticles to release isoniazid (BANIK et al., 2012, 2013; SAIKIA et al., 2015; SARMAH et al., 2015). In case of obtaining the polymeric particles, in general, first a polymer/clay compound is made by a solution method followed by the obtaining of nanoparticles using an emulsion agent. After the obtaining of nanoparticles, glutaraldehyde is usually used as a crosslinking agent. The polymers for this kind of application must be biocompatible and biodegradable, so its common use chitosan (BANIK et al., 2012; BANIK; RAMTEKE; MAJI, 2014), or some polymer derived from starch (BANIK et al., 2013) or even both (SAIKIA et al., 2015). Clay particles can be kept in water previously to facilitate their swelling in INH solution (SAIKIA et al., 2015).

Clay can influence the polymer particle's properties like their size, surface smoothness, the adsorption capacity, water swelling capacity, and the release rate. In general, micro and nanoparticles reduced size with the addition of MMT, and that occurs because clay particles anchor polymer chains, preventing their free movement, reducing their mobility. BANIK et al. (2012) noticed that the presence of MMT reduced the particle size and increased the INH incorporation. This also affects the surface of micro/nanoparticles that become rougher because polymer chains, are not capable of well

accommodation. According to (BANIK et al., 2013), the presence of clay increases nanoparticles' porosity due to hindering the movement of polymer chains. However, nanoparticles' porous are smaller and the superficial area is higher than free clay nanoparticles. That occurs because clay particles can cover these porous.

In general, the adsorption capacity is related to the swelling capacity as well as the release rate. SAIKIA et al. (2015) showed the importance of magnetic nanoparticles to the controlled release of drugs, and these particles must be coated by a biopolymer due to their natural aggregated state. They observed that the addition of MMT improved the incorporation of INH due to the high superficial area and a network with polymer chains helping to retain more INH. The swelling capacity is affected by MMT because these particles hinder water molecules onto the polymer chain; they act like a physical barrier blocking their entry in these particles. Higher swelling capacity reduces the adsorption capacity due to the fact water molecules solvate INH reducing the encapsulation. The release rate is affected because of it as well (BANIK et al., 2012, 2013; SAIKIA et al., 2015; SARMAH et al., 2015).

Regarding the use of the MMT carrier itself, it is commonly using a water dispersion method to obtain the nanohybrids MMT/INH. In these studies, ultraviolet-visible spectrophotometer (UV-vis) is used to verify the quantity of INH in water after the dispersion. This process can be influenced by pH, temperature, clay water swelling before having any contact to INH, time of particle contact with drug, and the concentration of the adsorbent and adsorbed. The previously preparation of MMT can vary depending on water dispersion of these particles and sonication or stirring or any kind of preparation unless the sieving (AKYUZ; AKYUZ, 2008), MMT can also be treated with another organic substance to increase the interlayer distance (SALIHI; GÜNDÜZ; BAŞTUĞ, 2019).

The incorporation of INH can be modeled by mathematical fitting and can be done studies about the adsorption kinetics and adsorption isotherms, as the INH releasing. (SALIHI; GÜNDÜZ; BAŞTUĞ, 2019) showed that the adsorption occurs basely by two mechanisms: interlayer diffusion and film diffusion; and the adsorption formed a monolayer of INH, the same was observed by (CARAZO et al., 2018a). And there are no differences among MMT and organo-MMT adsorption mechanisms. They also verified

that in acid pH the adsorption capacity increased, and the highest capacity occurred in pH around 4, when INH assumed its cationic form. Also, organic clays have molecules that can reduce MMT superficial charge, reducing electrostatic repulsion and interact with INH by hydrogen bonds, which improve MMT adsorption capacity.

The releasing of INH by MMT depends on temperature as well; the study developed by SUGUNALAKSHMI et al. (2014) indicates that the highest adsorption capacity occurs around 40°C. It was observed that when the concentration of MMT is higher than INH it improves the quantity of drug adsorbed. To study the mechanisms that are evolving to the releasing, some mathematical analyses are necessary like different modeling and verify how best the experimental data fit to each modeling. And it was observed that the major mechanism of releasing is diffusion. AKYUZ and AKYUZ (2008) observed that the interaction between INH and clay can be coordinated by exchangeable cations and the carboxyl group can interact with the water molecules that are present in clay particles' surface.

Halloysites nanotubes were used as nanocarriers for isoniazid by CARAZO (2019), the aqueous dispersion method used was like other authors, being a solution of water and halloysite added with a solution of INH in water, then stirred, sedimented, filtered, centrifuged, dried, and disaggregated. Result is a nanohybrid with an outer diameter of 90 nanometers. Further in vitro biocompatibility studies demonstrated the effectiveness of nanohybrid penetrating cell membranes and releasing the drug.

Expanded perlite, studied by DE ALMEIDA (2019), which is an aluminosilicate rich in SiO_2, was treated with ethanol and nitric acid, following similar methods as other authors, i.e., aqueous dispersion under constant stirring, filtered, dried, disaggregated, and characterized. The incorporation of isoniazid also followed the aqueous dispersion method with further drying. The resulting nanohybrid presented an average load of 41% in a weight basis, and then submitted to release experiments in simulated gastrointestinal environment.

While studying biomedical applications of magnetic particles for drug targeting delivery systems, SAIKIA (2015), described the advantages of magnetic properties and small size of iron oxide particles, coprecipitated with carboxymethyl starch and further loaded with isoniazid. The advantage of this system might be the delivery of the drug in

targeted areas when stimulated by an external magnetic field, resulting in a dosage reduction of the drug and improved efficiency. Results obtained by these researchers are highly promising.

The use of zeolites as a potential carrier for isoniazid has been investigated by SOUZA (2020), which is an alumina three-dimensional crystalline silicate, consisting of Si and/or Al tetrahedral, bonded to each other by common oxygen atoms, given its isomorphic substitution may generate a charge deficiency that is compensated by a cation exchange capacity, where the incorporation of isoniazid fits the system. The preparation of the nanohybrid followed the aqueous stirring system as used by other researchers, varying time, and concentration of reagents. Intercalations results situated in the average of 60 mg of isoniazid per gram of zeolite clay mineral.

Considering that most zeolite types suitable for pharmaceutical use are not naturally occurring, they are obtained by laboratory crystallization in aqueous media at controlled and specified conditions. SOUZA (2021), moving further of his previous mentioned research, incorporated isoniazid in a zeolite-faujasite type, following the same aqueous dispersion method. Results have been recently published and account for an average incorporation rate of 25 mg of isoniazid per gram of clay mineral, followed by controlled release curves within the expected profile in the gastrointestinal environment.

4 CURRENT STATUS / CONCLUSION

Mostly over the last ten years several research on the use of systems combining bentonites, kaolin, and isoniazid have been published and patents deposited. These systems are recognized as highly promising for the treatment of tuberculosis. Based on these successes, these systems are also being considered for the use as carriers for antineoplastic agents for the treatment of metastatic melanomas.

Another important market that may be addressed in the future is the veterinary market, which nowadays forbids the treatment of tuberculosis in cattle or other mammals. Whenever and whether this becomes a reality, it will represent an important economic milestone, especially in the cattle market.

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