PVP/Clay/Vanadium Oxide Nanocomposites Development and Characterization for Potential Use as Controlled Drug Release Matrix in Diabetes’ Treatment

Dario Barreto Reino de Almeida, Maria Inês Bruno Tavares

Abstract

Research in drug release field, nowadays, focuses on more efficient systems for better release of the drug and wider timespan of action, granting several benefits to the patient’s organism and to the industry. The present work aims on developing a matrix of polymer nanocomposite based on Polyvinylpyrrolidone (PVP), bentonite clay and two different vanadium oxides, via spray drying technique. The goal is to achieve a long and steady release of metformin hydrochloride in future formulations with this drug. Since either the nanocomposites or metformin hydrochloride is highly hydrophilic, it is most suited for a future formulation of tablets. For now, the nanocomposites obtained were characterized through Nuclear Magnetic Resonance (NMR), Scanning Electron Microscopy (SEM), X-Ray Diffraction (XRD), Thermogravimetric Analysis (TGA) and Fourier Transform Infrared Spectroscopy (FTIR). The SEM and XRD analysis portrayed a very amorphous and homogenized material. TGA and FTIR proved the insertion of the nanoparticles, thus granting to the new material a slightly higher thermal resistance. The NMR analysis, using T1H parameters, is key for determining the formulations would behave better for extending the resistance of the nanocomposite’s matrix with the drug in later dissolution of tablets.

Keywords

Polyvinylpirrolidone, Vanadium Pentoxide, Vanadium (IV) Oxide Sulfate Hydrate, Nanocomposite
1. Introduction

Nanostructured materials are part of a class of hybrid materials [1] that have characteristics that differentiate them from the composites due mainly to the greater aspect ratio that the nanometric particles have, providing a greater surface area. Because of this, the proportions of these fillers are smaller than those used in the production of micrometric composites, generating materials with different density and strength than those of the materials commonly used [2] [3] [4]. When one of the phases composing the nanostructured material is a polymer, it is said that this is a polymer nanocomposite, in which the dispersion of the nanoparticle in the polymer matrix is the main factor for determining the final properties of the material [5] [6]. The production of polymeric nanocomposites is possible with almost all types of polymers with the proper methods [1]. Lately, the use of hybrid nanomaterials for drug release has been very intense, due to the characteristics of the new materials and the relative simplicity that these systems can be prepared and employed [7].

For several years, research in the field of drug formulation focused on the search for systems that would make the release of these drugs prolonged after being given. The motives, among others, that have led to the formulation of sustained drug delivery systems are based on the desire to obtain highly water soluble compounds capable of releasing slowly, targeting such compounds to the target tissues or cells, to achieve adequate release rates at given reduce the number of daily administrations and improve reliability while minimizing side effects. As with immediate release formulations, oral administration is the primary form of delivery of sustained release drugs to the body as well. Due to the easy availability, there are better adjustment of the doses administered, better acceptance by patients and cost-efficient production, among other reasons [7] [8] [9] [10] [11]. Among these systems, especially those that do controlled diffusion and dissolution, those of hydrophilic matrices stand out. Some important characteristics of these matrices include the fact that they are of simple formulation, of easy and inexpensive production, besides their excellent in vitro-in vivo correlation. Another important feature and advantage is the possibility of associating high molecular weight hydrophilic drugs with hydrophilic polymer matrices, which are the most widely used controlled release systems in a few years more recently [12] [13] [14] [15]. However, these systems are also subject to problems. One of the major problems of formulating such systems is achieving an adequate rate of drug release so that drug concentrations in the blood remain within the therapeutic range and that this occurs within the desired time. Equally worrying in the case of hydrophilic matrices, when it comes to drugs with low solubility in water, low dissolution is a real problem. In order to overcome the hydrophilic polymer barrier and to make the drug more soluble in the solvent, it is possible to use molecular engineering in the nanocomposite formulation, so that the availability of the drug is greater, compensating for its naturally low solubility [10] [15] [16] [17] [18].

Polyvinylpyrrolidone (PVP) is a biocompatible and innocuous polymer in the
body, although it originates from an extremely toxic monomer, whose main characteristics are its high hygroscopicity and solubility in water and other polar solvents. What promotes great ease of forming polymer films, adhesives, coatings, among others. It is widely used in pharmaceutical formulations excipients and antiseptic solutions when dry, it appears as a flocculent white powder, naturally suitable for tableting, which is widely used as pharmaceutical excipients by the pharmaceutical industry. Due to its high solubility, PVP is especially employed in more immediate release formulations, since in aqueous medium the polymer matrix is solubilized in a short time, making the drug readily available in the body. For use of the same polymer in sustained or controlled release formulations, other strategies should be addressed [18] [19] [20] [21]. Given the difficulties presented by using only PVP in these systems, these can be solved in several ways. One of these is using this polymer in systems of nanostructured materials [22] [23].

A lot of recent research has been devoted to the development of nanostructured materials containing inorganic fillers dispersed in a polymer matrix. However, these new nanostructured materials should first undergo through tests for safety and effectiveness. Among nanoparticles, montmorillonite clay is safe for biomedical applications, since this clay is already used in pharmaceutical preparations. Bentonite is plastic clay consisting mostly of montmorillonite, a natural clay of the smectite group. It is a type 2:1 lamellar silicate (2 silicon tetrahedrons:1 aluminum octahedron). Regarding its microstructure, the lamellae have diameters between approximately 100 - 200 nm and thickness of 1 nm. This clay is used as a functional excipient in tablets due to its ability to form gels at low concentrations by swelling in water, and it is also used as a binder and disintegrate. For these reasons, bentonite is often employed to produce nanostructured microparticles [24]-[30].

Some metallic oxides are known to be used for treating diabetes, as well as for other diseases like cancer, parasitosis, and so on. Among them, vanadium oxides are the most utilized for treating diabetes; since it presents important characteristics for controlling that condition, such as inhibiting lipolysis process, lowering the glucose levels in the blood stream, and stimulating insulin secretion [15] [31] [32].

To produce such kind of nanostructured microparticles for controlled drug release, the spray-drying technique appears as an interesting alternative to achieve homogeneously dispersed materials. Specially for further production of tablets, which are a more convenient means of administration. With good dosage precision, ease to be manufactured, product stability when compared to liquids and inviolability compared to capsules. Tablets are preferably manufactured by direct compression given their simplicity, continuous nature and financial advantages [33]-[38].

The spray-drying is a very efficient method for producing powders, granules, agglomerates or crystals from a liquid phase, which may come from solutions,
dispersions, emulsions or suspensions. The method is especially efficient for the
formation of microparticles and nanoparticles, besides being able to form par-
icles with varied porosities, having a wide potential of applications [37] [39].
This technique consists of three stages, nominally: atomization, dehydration or
drying and collection of the material. In atomization, the liquid phase is directed
by a peristaltic pump to the atomizer, in which it encounters a strong flow from
the air pump, and both are designed by the nozzle of the atomizer to the drying
chamber. In this chamber, the strong flow of hot air quickly removes almost all
the solvent, forming vapor, thanks to the previous atomization and leaving the
solid fraction of the original liquid phase. This resulting solid, usually a very fine
powder, is directed to the cyclone where the separation of particles from the air-
flow occurs and where the solid is collected. It is a very versatile technique, c a-
pable of generating final products with different morphologies only by changing
the operating parameters, but also so it requires an experienced operator and at-
tentive to all these parameters such as feed rate, drying gas inlet temperature,
drying gas flow, atomizing pressure, among others less expressive [37] [40] [41].

Due to the huge number of people affected by Diabetes mellitus in the world
nowadays and the chronical characteristics of its symptoms, difficulties for the
patient to begin, adhere and maintain the treatment, a very recurrent hydrophil-
ic drug was chosen to be part of the object this study: Metformin hydrochloride
[22] [42].

Thus, the main objective of this paper is to present the development, charac-
terization and evaluation of the effects of different formulations for a polymer
nanocomposite matrix based on polyvinylpyrrolidone, sodium bentonite clay,
v anadium oxide and vanadium (IV) oxide sulphate as nanoparticles, for later
study of the release of metformin hydrochloride for the treatment of diabetes.
Relying on the various analytical tools, especially the low-spin NMR spin-network
relaxation time to select the best formulations for benchmarking the drug release
potential in dissolution assays for the later produced tablets [22] [23] [43] [44].

2. Experimental

2.1. Materials

For this work, the following reagents and products were used to produce the dif-
ferent formulations of nanocomposites:

- Polyvinylpyrrolidone K-30 average molecular weight 40,000 g/mol, obtained
  from Fulka Analytical.
- Sodic bentonite clay NT 25, obtained from Bentonit União Nordeste. This
  clay is a natural, unmodified bentonite, with surface area of 139 m²·g⁻¹ and
  cation exchange capacity of 0.8 mEq/g.
- Pure Metformin hydrochloride, approximately 78% Metformin in mass. Ob-
  tained from Norida Biotech, China.
- Vanadium pentoxide, from Merck.
- Vanadium (IV) oxide sulphate hydrate, from Merck.
2.2. Methods

2.2.1. PVP Analysis
PVP was received as a donation from UFRJ department of pharmacy. PVP sample and the nanocomposites obtained with it were evaluated through Fourier transform infrared spectroscopy, X-ray diffraction, thermogravimetric analysis, scanning electron microscopy and low field nuclear magnetic resonance.

2.2.2. Preparation of the Nanocomposites
The nanocomposites were prepared via solution using Mili-Q grade purified water as the solvent. The tests for the blends consisted of solutions with final 5 g of the mixture of polyvinylpyrrolidone K-30, sodium bentonite clay, vanadium pentoxide and vanadium (IV) oxide sulphate hydrate. So that the clay and the vanadium oxides were presented in proportions of, respectively, 2%, 0.1%, 0.1% of the final mass intended for these blends. This data will be better detailed in the example of Table 1. It shows how one of the formulations was done, but for the others studied, it was just a matter of adjusting the mass of PVP accordingly, in order to reach final mass of 5 g. Using Erlenmeyers to separately disperse the nanoparticles and polymer in Mili-Q water. These mixtures were stirred for 4 hours in Erlenmeyer with magnetic stirring.

In a more advanced phase of this study, at the same time, in another Erlenmeyer, were dissolved in 100 ml of Mili-Q water, 5 g of metformin hydrochloride. It had also undergone magnetic stirring for 4 hours separately. After this initial time, all the Erlenmeyers were poured into a Beaker under magnetic stirring for another 1 hour, in order to promote a good interaction between the components before undergoing the spray dryer treatment.

The spray-dryer parameters were configured considering the glass transition temperatures and/or melting point of each component of the nanocomposite, so as not to scorch the material, being only enough to evaporate all the solvent. These parameters were: peristaltic pump flow of 0.5 L/h, inlet temperature 125˚C, outlet temperature 89˚C, spray nozzle 1 mm, compressed air flow 30 L/h.

After collecting all the powdered material, it proceeded to analysis.

2.2.3. Nanocomposites Characterization
1) Thermogravimetric analysis
The analyses of the samples were made to evaluate the thermal stability of the obtained nanocomposites. They occurred in an inert nitrogen atmosphere with a constant heating rate of 10˚C/min, the heating range was 0˚C to 700˚C, the sample masses were approximately 8 mg. The analysis was obtained with an accuracy of ±2˚C.

Table 1. Example of proportions used to produce nanocomposites.

| Mili-Q water (Volume in ml for the nanoparticles and PVP) | PVP (% of mass and mass in grams) | Bentonite (% of mass and mass in grams) | Vanadium pentoxide (% of mass and mass in grams) | Vanadium (IV) oxide sulphate hydrate (% of mass and mass in grams) |
|------------------------------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------------------|-------------------------------------------------|
| 15 ml/85ml                                                 | 97.8%/4.89g                       | 2%/0.10g                               | 0.1%/0.005g                                   | 0.1%/0.005g                                     |
2) Fourier transform infrared spectroscopy

Samples behavior was verified in the intermediary portion of infrared spectrum. Aiming to observe the spectrum bands variations due to the dispersion/interaction between clay nanoparticles and the polymeric matrix. Conditions applied were: 20 scannings with 4 cm⁻¹ resolution, throughout all the spectrum from 4000 cm⁻¹ to 400 cm⁻¹.

3) X-rays diffraction analysis

The nanocomposites samples obtained, as well as the pristine polymer, were evaluated through x-ray diffraction analysis as powdered samples. These analyses were executed with CuKα (α = 1.5418 Å) radiation emission, at room temperature in 30 kV and 15 mA, with 2θ varying from 2 to 60 degrees and scanning speed at 0.05˚/s.

4) Scanning electron microscopy

Analysis of scanning electron microscopy were conducted to study the morphology of the microparticles containing nanocomposites, observing their distribution, uniformity, porosity resulting from the spray-drying technique. The scanning electron microscope was equipped with field emission. Increases of up to 200,000 times were performed with 10 kV of voltage, and the ideal increase in visualization of the particle morphology stabilized around 5000 times. The samples were covered with gold, to allow the analysis of the polymeric materials.

5) NMR characterization in the time domain

NMR was employed to study characteristics such as fluidity or stiffness and how the interaction with the nanoparticles interferes with the polymer. For the determination of mean spin-lattice relaxation times (T₁H) of the hydrogen nuclei, were used the inversion-recovery pulse sequence (p180˚x - τ - p90˚x) with pulse duration of 90˚ of 7.5 μs, logarithmic time list between the pulses 0.01 - 5000 ms, 40 points, 4 scans, 1 s of recycle delay and 2% gain of the receiver.

3. Results and Discussion

3.1. Thermogravimetric Analysis

Six compositions of the nanocomposites were compared regarding their thermal resistance, and their maximum degradation temperatures had a very similar degradation behavior in all compositions. There was a seventh composition of PVP with V₂O₅, but unfortunately that data was lost. Nevertheless, the values were around the average of these portrayed as in Table 2.

Table 2. Thermal behavior of nanocomposites.

| Sample           | Humidity (%) | T onset (˚C) | T offset (˚C) | T peak (˚C) | Residue (%) |
|------------------|--------------|--------------|--------------|-------------|-------------|
| PVP VOSO4 V2OS5  | 17           | 382          | 445          | 423         | 6           |
| PVP Bentonite VOSO4 V2OS5 | 17           | 382          | 442          | 422         | 4           |
| PVP Bentonite VOSO4 | 18           | 381          | 443          | 423         | 4           |
| PVP Bentonite V2OS5 | 19           | 385          | 446          | 424         | 5           |
| PVP VOSO4        | 19           | 381          | 443          | 423         | 3           |
| PVP Bentonite   | 19           | 387          | 445          | 423         | 4           |

DOI: 10.4236/msa.2019.1012056
Figure 1 shows the thermal degrading events of the nanocomposite of PVP and 2% bentonite clay by thermal gravimetric analysis.

From the TGA curves (Figure 1) and the data in Table 2, it is possible to conclude that, although the insertion of these nanoparticles in the system makes it slightly more thermally resistant, all the compositions had a very similar thermal behavior.

3.2. Fourier Transform Infrared Spectroscopy

Figure 2 shows the FTIR spectra of the nanocomposites.

From the analysis of the infrared spectra of all nanocomposite’s formulations produced, it was observed that the bands, from 500 to 1750 cm\(^{-1}\), refer to the polymer and the nanoparticles were detected. The slight disturbances in higher wavelengths refer most likely to residual water, due to hygroscopicity. Corroborating the behavior observed in the TGA in relation to uniformity between the systems.

3.3. X-Ray Diffraction Analysis

Figure 3 shows the profiles of the nanocomposites diffractograms in comparison to each other.

The analysis of the diffractograms revealed that these materials are predominantly amorphous in all compositions, both for the nanocomposites without drug and for the same with the addition of drug. The different insertion of either sodium bentonite and/or the vanadium oxides into the PVP matrix gave rise to a very low diffraction peak around 2.5° in 2θ, varying very little among the nanocomposites’ compositions, indicating the formation of mixed nanocomposites containing exfoliated part and intercalated part of clay. In all materials, including the pure polymer, the presence of diffraction peaks occurs around 12.5° and 22°.
That pattern of both exfoliated and intercalated material is most welcome for future compositions that will have the drug inserted, since that morphology is intended for controlled release scenarios. Crystalline materials tend to be those of stronger molecular stability, making it less prone for anchoring of new substances such as an external drug.

3.4. Scanning Electron Microscopy

Figure 4 and Figure 5 show the Scanning Electron Microscopies of PVP in different magnifications and treatments. Figure 6 refers to the PVP system with 2% sodium bentonite.

The micrographs of Figure 4 and Figure 5 represent PVP in different magnifications and treatments. In these first two SEM images, the pure PVP K-30 is shown, with no treatment beyond the gold coating required for microscopy. It is noted that there is an extreme disorganization of the microparticles, with completely irregular shapes and sizes. The second image (Figure 5) is a projection of the same field of Figure 4, but with the same magnification practiced in the third image (5000×) (Figure 6). In this way, it is observed that the treatment by
the spray-dryer can uniformize the microparticles and give them a porous surface, thus, increasing the relative surface area for interaction with the drug, for example.

**Figure 4.** Scanning electron microscopies of PVP in different magnifications and treatments.

**Figure 5.** Scanning electron microscopies of PVP in different magnifications and treatments.

**Figure 6.** Image refer to the PVP nanocomposite matrix with 2% sodium bentonite.
Figure 6 image refers to the PVP nanocomposite matrix with 2% sodium bentonite. It is possible to perceive greater clarity in the microparticles in it, revealing a good aggregation of the polymer chains with the clay. It is also perceived that the material becomes more regular in its dimensions and remains porous.

Although all compositions with the vanadium oxides were unable to be scanned, due to technical difficulties of the microscope, luckily enough, there was opportunity to make such of the drug alone, and of it inserted on this nanocomposite. It is stated in the experimental part, as described in Table 1.

Micrographs of the nanocomposite matrix with the drug show that it coated the surface of the microparticles, which is a very interesting and important fact for the study in question.

3.5. NMR Characterization in the Domain of Time

Figure 7 shows the domain curves obtained from the spin-lattice relaxation times of the PVP nanocomposites.

NMR relaxation times were used to understand the formation of molecular organization through the molecular dynamics of the studied materials. It shows the comparison of the seven domain curves of the different nanocomposites. There is a noticeable difference in the relaxation times for $T_{1,1}H$ and $T_{1,2}H$. In Figure 7, relaxation time values for compositions containing 2% sodium bentonite and vanadium pentoxide as nanoparticles had the longest time (228 ms) for recovering from the excited state. On the other hand, the composition with the same 2% sodium bentonite, but the other vanadium oxide (VOSO₄) had the shortest time (170 ms) for recovering from the excited state, amongst the formulations with any vanadium oxide. These are being taken mostly in consideration due to the possible therapeutical effect on hyperglycemia of the vanadium oxides, when combined with metformin hydrochloride, although with only the
2% bentonite composition, it was even shorter (144 ms). Those, with lower T$_{1H}$ times would be indicated for faster release systems, due to the intermolecular interactions, and the higher T$_{1H}$ time formulations, for the opposite purpose. Still, it is also desirable that the peak of relaxation has a wider base, so that it will mean that there are regions of the material that will release controllably the ensnared drug at different and continuous moments through the extended release process. For these cases, the formulations with both vanadium oxides, with or without sodium bentonite, are the most desirable to pursue [43].

4. Conclusion

Thermogravimetric analysis showed that the nanocomposites in all the formulations presented similar resistance to thermal degradation among the different samples. The infrared spectroscopy, intended to evaluate the insertion of the drug in the nanocomposite chains in later readings, displayed very similar behavior for the samples analyzed. X-ray diffractograms of the nanocomposites revealed that the material is predominantly amorphous, as expected. Scanning electron microscopy showed that, not only after treating the samples via spray-dryer, the PVP microparticles had a more uniform, consistent and defined appearance, especially in the nanocomposites, but also with the insertion of metformin hydrochloride in the system has altered the morphological aspect of materials, presenting itself effectively in a well dispersed and abundant shape in nanocomposite microparticles. The analysis of the values of the relaxation times and the shape of the domain curves show that there was the formation of mixed nanocomposites, containing both intercalated and exfoliated part. Only the NMR relaxometry displayed relevant information regarding the real interaction between the different materials, due to the collective movements of the polymer chains in the systems. The most heterogeneous, and suitable for controlled drug release, were the samples containing both vanadium oxidation states, as they promote a synergic effect, controlling the molecular organization, displaying wider baseline in the distribution in the domain curves. Those matrices could potentially be applied for controlled release with other hydrophilic drugs, as well. And it is imperative to incorporate metformin hydrochloride to all the samples studied so far, to further confirm the anticipated synergy in hypoglycemic therapy for the drug and the vanadium oxides in the next experiments.

Acknowledgements

The authors would like to thank to the Brazilian agencies, CNPq, FAPERJ and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) Finance Code 001.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.
References

[1] Kumar, A.P., Depan, D., Tomer, N.S. and Singh, R.P. (2009) Nanoscale Particles for Polymer Degradation and Stabilization—Trends and Future Perspectives. Progress in Polymer Science, 34, 479-515. https://doi.org/10.1016/j.progpolymsci.2009.01.002

[2] Velmurugan, R., Jeyaprakash, P. and Balaganesan, G. (2008) Damping Study of Hybrid Nanocomposites by Low Velocity Impact. Proceedings of International Conference on Aerospace Science and Technology, Bangalore, India, 26-28.

[3] Chandrasekaran, S., Faiella, G., Prado, L.A.S.A., Trölle, F., Mühlaupt, R. and Schulte, K. (2013) Thermally Reduced Graphene Oxide Acting as a Trap for Multi-wall Carbon Nanotubes in Bi-Filler Epoxy Composites. Composites: Part A, 49, 51-57. https://doi.org/10.1016/j.compositesa.2013.02.008

[4] Maderuelo, C., Zarzuelo, A. and Lanao, J.M. (2011) Critical Factors in the Release of Drugs from Sustained Release Hydrophilic Matrices. Journal of Controlled Release, 154, 2-19. https://doi.org/10.1016/j.jconrel.2011.04.002

[5] Miranda, A., Millán, M. and Caraballo, I. (2006) Study of the Critical Points of HPMC Hydrophilic Matrices for Controlled Drug Delivery. International Journal of Pharmaceutics, 311, 75-81. https://doi.org/10.1016/j.ijpharm.2005.12.012

[6] Huang, X. and Brazel, C.S. (2001) On the Importance and Mechanisms of Burst Release in Matrix-Controlled Drug Delivery Systems. Journal of Controlled Release, 73, 121-136. https://doi.org/10.1016/S0168-3659(01)00248-6

[7] Homayouni, A., Sadeghi, F., Varshosaz, J., Garekani, H.A. and Nokhodchi, A. (2014) Comparing Various Techniques to Produce Micro/Nanoparticles for Enhancing the Dissolution of Celecoxib Containing PVP. European Journal of Pharmaceutics and Biopharmaceutics, 88, 261-274. https://doi.org/10.1016/j.ejpb.2014.05.022

[8] Büler, V. (2005) Polyvinylpyrrolidone Excipients for Pharmaceuticals: Povidone, Crospovidone and Copovidone. Springer, Berlin, Heidelberg, New York.

[9] Koczur, K.M., Mourdikoudis, S., Polavarapu, L. and Skrabalak, S.E. (2015) Polyvinylpyrrolidone (PVP) in Nanoparticle Synthesis. Dalton Transactions, 44, 17883-17905. https://doi.org/10.1039/C5DT02964C

[10] Sapir, L., Stanley, C.B. and Harries, D. (2016) Properties of Polyvinylpyrrolidone in a Deep Eutectic Solvent. Journal of Physical Chemistry A, 120, 3253-3259. https://doi.org/10.1021/acs.jpca.5b11927

[11] Monteiro, M.S.S.B., Rodrigues, C.L., Miguez, E. and Tavares, M.I.B. (2016) Development of Polycaprolactone/Poly (Vinyl Alcohol)/Clay Microparticles by Spray Drying. Materials Sciences and Applications, 7, 575. https://doi.org/10.4236/msa.2016.710048

[12] Fedorova, E.V., Buryakina, A.V., Zakharov, A.V., Filimonov, D.A., Lagunin, A.A. and Poroikov, V.V. (2014) Design, Synthesis and Pharmacological Evaluation of Novel Vanadium-Containing Complexes as Antidiabetic Agents. PLoS ONE, 9, e100386. https://doi.org/10.1371/journal.pone.0100386

[13] Pessoa, J.C., Etcheverry, S. and Gambino, D. (2015) Vanadium Compounds in Medicine. Coordination Chemistry Reviews, 301-302, 24-48. https://doi.org/10.1016/j.ccr.2014.12.002

[14] Gohel, M.C. and Jogani, P.D. (2005) A Review of Co-Processed Directly Compressible Excipients. Journal of Pharmacy and Pharmaceutical Sciences, 8, 76-93.

[15] Agnihotri, S.A. and Aminabhavi, T.M. (2004) Controlled Release of Clozapine through Chitosan Microparticles Prepared by a Novel Method. Journal of Con-
trolled Release, 96, 245-259. https://doi.org/10.1016/j.jconrel.2004.01.025

[16] Vanhoorne, V., Peeters, E., Van Snick, B., Remon, J.P. and Vervaet, C. (2014) Crystal Coating via Spray Drying to Improve Powder Tabletability. European Journal of Pharmaceutics and Biopharmaceutics, 88, 939-944. https://doi.org/10.1016/j.ejpb.2014.10.018

[17] De Fronzo, R.A., Hissa, M.N., Garber, A.J., Gross, J.L., Duan, R.Y., Ravichandran, S. and Chen, R. (2009) The Efficacy and Safety of Saxagliptin When Added to Metformin Therapy in Patients with Inadequately Controlled Type 2 Diabetes on Metformin Alone. Diabetes Care, 32, 1649-1655. https://doi.org/10.2337/dc08-1984

[18] Aguiar, M.R.M.P. and Novaes, A.C. (2002) Remoção de metais pesados de efluentes industriais por aluminossilicatos. Química Nova, 25, 1145-1154. https://doi.org/10.1590/S0100-40422002000700015

[19] Ahmed, E.M. (2013) Hydrogel: Preparation, Characterization, and Applications. Journal of Advanced Research, in press.

[20] Alexandre, M. and Dubois, P. (2000) Polymer-Layered Silicate Nanocomposites: Preparation, Properties and Uses of a New Class of Materials. Materials Science and Engineering: Reports, 28, 1-63. https://doi.org/10.1016/S0927-796X(00)00012-7

[21] Bergaya, F. and Lagaly, G. (2001) Surface Modification of Clay Minerals. Applied Clay Science, 19, 1-3. https://doi.org/10.1016/S0169-1317(01)00063-1

[22] Castañeda, L., Alonso, J.C., Ortiz, O., Andrade, E., Saniger, J.M. and Bañuelos, J.G. (2003) Spray Pyrolysis Deposition and Characterization of Titanium Oxide Thin Films. Materials Chemistry and Physics, 77, 938-944. https://doi.org/10.1016/S0254-0584(02)00193-1

[23] Costa, A.C.F.M., Vilar, M.A., Lira, H.L., Kiminami, R.H.G.A. and Gama, L. (2006) Síntese e caracterização de nanopartículas de TiO2. Cerâmica, 52, 255-259. https://doi.org/10.1590/S0366-69132006000400007

[24] Das, D. and Pal, S. (2015) Dextrin/poly (HEMA): pH Responsive Porous Hydrogel for Controlled Release of Ciprofloxacin. International Journal of Biological Macromolecules, 72, 171-178. https://doi.org/10.1016/j.ijbiomac.2014.08.007

[25] Deng, H. and Lei, Z. (2013) Preparation and Characterization of Hollow Fe3O4/SiO2@PEG-PLA Nanoparticles for Drug Delivery. Composites Part B: Engineering, 54, 194-199. https://doi.org/10.1016/j.compositesb.2013.05.010

[26] Dolenc, A., Kristl, J., Baumgartner, S. and Planinšek, O. (2009) Advantages of Celecoxib Nanosuspension Formulation and Transformation into Tablets. International Journal of Pharmaceutics, 376, 204-212. https://doi.org/10.1016/j.ijpharm.2009.04.038

[27] Ferreira, L., Vidal, M.M., Geraldes, C.F.G.C. and Gil, M.H. (2000) Preparation and Characterization of Gels Based on Sucrose Modified with Glycidil Methacrylate. Carbohydrate Polymers, 41, 15-24. https://doi.org/10.1016/S0144-8617(99)00064-8

[28] Ferrero, C., Massuelle, D., Jeannerat, D. and Doelker, E. (2008) Towards Elucidation of the Drug Release Mechanism from Compressed Hydrophilic Matrices Made of Cellulose Ethers. I. Pulse-Field-Gradient Spin-Echo NMR Study of Sodium Salicylate Diffusivity in Swollen Hydrogels with Respect to Polymer Matrix Physical Structure. Journal of Controlled Release, 128, 71-79. https://doi.org/10.1016/j.jconrel.2008.02.006

[29] Jain, S. and Datta, M. (2014) Montmorillonite-PLGA Nanocomposites as an Oral Extended Drug Delivery Vehicle for Venlafaxine Hydrochloride. Applied Clay Science, 99, 42-47. https://doi.org/10.1016/j.clay.2014.06.006
[30] Kaufhold, S., Dohrmann, R., Ufer, K. and Meyer, F.M. (2002) Comparison of Methods for the Quantification of Montmorillonite in Bentonites. Applied Clay Science, 22, 145-151. https://doi.org/10.1016/S0169-1317(02)00131-X

[31] Li, X.L. and Jasti, B.R. (2006) Design of Controlled Release Drug Delivery Systems. McGraw-Hill, New York.

[32] Lv, F., Fu, L., Giannelis, E.P. and Qi, G. (2014) Preparation of γ-Fe₃O₄/SiO₂-Capsule Composites Capable of Using Drug Delivery and Magnetic Targeting System from Hydrophobic Iron Acetylacetonate and Hydrophilic SiO₂-Capsule. Solid State Sciences, 34, 49-55. https://doi.org/10.1016/j.solidstatesciences.2014.05.006

[33] Mano, E.B. and Mendes, L.C. (1999) Introdução a Polímeros. 2nd Edition, Edgard Blücher, São Paulo.

[34] Narasimharao, R., Anusha Reddy, M., Swetha Reddy, N., Divyasagar, P. and Kërthana, K. (2011) Design and Evaluation of Metformin Hydrochloride Extended Release Tablets by Direct Compression. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2, 1118-1133.

[35] Oliveira, M.J.A., Estêfânia, O.S., Lúcia, M.A.B., Regina, M., Amato, V.S., Lugão, A.B. and Parra, D.F. (2014) Influence of Chitosan/Clay in Drug Delivery of Glucantime from PVP Membranes. Radiation Physics and Chemistry, 94, 194-198. https://doi.org/10.1016/j.radphyschem.2013.05.050

[36] Rigo, V.A., Lara, L.S. and Miranda, C.R. (2014) Energetics of Formation and Hydratation of Functionalized Silica Nanoparticles: An Atomistic Computational Study. Applied Surface Science, 292, 742-749. https://doi.org/10.1016/j.apsusc.2013.12.042

[37] Rodrigues, L.A.S., Figueiras, A., Veiga, F., Freitas, R.M., Nunes, L.C.C., Silva Filho, E.C. and Leite, C.M.S. (2013) The Systems Containing Clays and Clay Minerals from Modified Drug Release: A Review. Colloids and Surfaces B: Biointerfaces, 103, 642-651. https://doi.org/10.1016/j.colsurfb.2012.10.068

[38] Scientists Solutions. http://www.scientistsolutions.com/forum/protein-chemistry-assay-development-protocols/10x-pbs-recipe

[39] Silva, E.P., Sitta, D.L.A., Fragal, V.H., Cellet, T.S., Mauricio, M.R., Garcia, F.P., Nakamura, C.V., Guilherme, M.R., Rubira, A.F. and Kunita, M.H. (2014) Covalent TiO₂/Pectin Microspheres with Fe₃O₄ Nanoparticles for Magnetic Field-Modulated Drug Delivery. International Journal of Biological Macromolecules, 67, 43-52. https://doi.org/10.1016/j.ijbiomac.2014.02.035

[40] Simo, C., Cifuentes, A. and Gallardo, A. (2003) Drug Delivery Systems: Polymers and Drugs Monitored by Capillary Electromigration Methods. Journal of Chromatography B, 797, 37-49. https://doi.org/10.1016/S1570-0232(03)00430-6

[41] Son, J.S., Kim, K.H. and Kwon, T.Y. (2012) Drug Delivery from Titanium Surface Using Biodegradable Nanoparticle Carriers. Materials Letters, 89, 129-132. https://doi.org/10.1016/j.matlet.2012.08.084

[42] Thostenson, E.T., Li, C. and Chou, T.-W. (2005) Nanocomposites in Context. Composites Science and Technology, 65, 491-516. https://doi.org/10.1016/j.compscitech.2004.11.003

[43] Tiwari, S.B. and Rajabi-Siahboomi, A.R. (2008) Extended-Release Oral Drug Delivery Technologies: Monolithic Matrix Systems, Drug Delivery Systems. In: Jain, K.K., Ed., Methods in Molecular Biology; Humana Press, Totowa, NJ, 217-243. https://doi.org/10.1007/978-1-59745-210-6_11

[44] Wang, T., Jiang, H., Wan, L., Zhao, Q., Jiang, T., Wang, B. and Wang, S. (2015) P-
Potential Application of Functional Porous TiO₂ Nanoparticles in Light-Controlled Drug Release and Targeted Drug Delivery. *Acta Biomaterialia*, 13, 354-363. https://doi.org/10.1016/j.actbio.2014.11.010