Analysis of excipients used in capsules prepared in magistral pharmacies of the Baixada Fluminense-RJ

Análise de excipientes utilizados em cápsulas preparadas em farmácias magistrais da Baixada Fluminense-RJ

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ABSTRACT
Magistral pharmacies currently represent an important segment in the Brazilian drug market. It is known that in magistral preparations, drugs are associated with excipients, which are substances that have different characteristics and functions, helping in pharmaceutical formulations. The inappropriate use of these adjuvants can cause interactions with the drug and thus compromise its bioavailability and therapeutic efficacy. Based on this fact, the objective of this work was to evaluate the excipients used in magistral preparations, in the pharmaceutical form of capsules, in magistral pharmacies in Baixada Fluminense-RJ. Data collection was carried out through a questionnaire that was filled out by the pharmacist responsible for each researched establishment, to which the excipient used for the preparation of each mentioned drug was selected. Based on the results exposed in the present study, it was concluded that there is a high error rate in the selection of excipients used in the evaluated formulations of the main manipulated drugs, highlighting the use of adjuvants that have incompatibilities with the analyzed drugs. Considering that most medications, being Fluoxetine, Losartan, Risperidone, Tadalafil, Atenolol, Enalapril, Clonazepam and Hydrochlorothiazide, are widely prescribed, it is necessary to give due importance to the formulations, to guarantee the safety and quality of the magistral products.

Keywords: Excipients, Capsules, Magistral Pharmacy.

RESUMO
Atualmente as farmácias de manipulação representam um importante segmento no mercado brasileiro de medicamentos. Sabe-se que nas preparações magistrais, os fármacos estão associados a excipientes, que são substâncias que apresentam características e funções distintas, auxiliando nas formulações farmacêuticas. A utilização inadequada desses adjuvantes pode ocasionar interações com o fármaco e assim comprometer a sua biodisponibilidade e eficácia terapêutica. Baseado neste fato, o objetivo deste trabalho foi avaliar os excipientes utilizados em preparações magistrais, sob a forma farmacêutica de cápsulas, em farmácias de manipulação da Baixada Fluminense. A coleta de dados deu-se por meio de um questionário que foi preenchido pelo farmacêutico responsável de cada estabelecimento pesquisado, ao qual era selecionado o excipiente utilizado para o preparo de cada fármaco citado. Com base nos resultados expostos

no presente trabalho, concluiu-se que há um alto índice de erro na seleção dos excipientes utilizados nas formulações avaliadas dos principais medicamentos manipulados, destacando o uso de adjuvantes que apresentam incompatibilidades com os fármacos analisados. Considerando que a maioria dos medicamentos citados, sendo eles a fluoxetina, losartana, risperidona, tadalafila, atenolol, enalapril, clonazepam e hidroclorotiazida, são amplamente prescritos, é necessário dar a devida importância às formulações, para assim garantir a segurança e qualidade dos produtos magistrais.

Palavras-chave: Excipientes, Cápsulas, Farmácia magistral.

1 INTRODUCTION

Over time, master pharmacies have undergone many changes to conform to legislation and quality criteria. This sector has had a high growth over the years, leading to increased demand for manipulated medicines. According to 2018 data from the Federal Council of Pharmacy, in Brazil there are about 8,300 pharmacies with manipulation (FERREIRA, 2008; MIGUEL *et al*., 2002).

In Brazil, compounding pharmacies, unlike other countries, offer varied types of drugs, even those that are made available by the pharmaceutical industry, usually with lower values, thus representing an important segment in the Brazilian drug market (FERREIRA, 2008; PINHEIRO, 2008). Manipulated drugs have several advantages over industrialized ones, such as the possibility of choosing the most appropriate pharmaceutical form for their condition and allowing adjustments of doses individualized to the needs of each patient. However, there are a number of objections that hinder the development of this sector, the most prominent being the lack of effective supervision regarding compliance with current standards. This generates a concern on the part of both health professionals and consumers (FRAZON & SILVESTRIN, 2010; PEREIRA *et al*., 2016).

Among all solid pharmaceutical forms, the most produced in the masterful pharmacy are the capsules, these are widely used because they have a good acceptance by patients, in addition to presenting several advantages when compared to other pharmaceutical presentations, among them we can highlight the ease of manipulation, possibility of replacing other pharmaceutical forms with smaller size and volume, mask unpleasant organoleptic properties, among others (BARBOSA, 2017; AULTON, 2005; BRAZIL, 2012). In these preparations, the drugs, in the vast majority of the times, are associated with excipients, which are substances that directly help the composition, besides presenting characteristics and properties distinct from the drugs (SOUZA, 2009; RAMOS & MORAIS, BARBOSA, 2017). Excipients are substances that do not have a therapeutic effect, that is, they are inactive ingredients, used to improve the physicochemical and organoleptic characteristics of drugs, in addition to ensuring their stability. In different formulations can be used several types of excipients, the choice will depend on the function required for the drug. These substances have several functionalities, among them we can mention: dyes, emulsifiers,

stabilizers, flavorings, preservatives, sweeteners, antioxidants, thickeners, among others. (BARBOSA, 2017; BALBANI, 2006). The pharmacist should always opt for the excipient that does not have any type of interaction with the drug, that is, they must be compatible to generate a safe, stable, and effective drug. Taking into account that some drugs have diverse characteristics, both compatibility and physico-chemical, the choice of excipients suitable for them is fundamental (ANSEL, POPOVICH & ALLEN JR, 2000; Moreton, 2010). The incorrect use of excipients may compromise the bioavailability and therapeutic effect of the drug. It is known that each type of excipient has different characteristics, in which each substance acts in different ways in the formulation and can assist in the solubilization of the drug or modifying the release of the same in the gastrointestinal tract, or even delay the dissolution of the drug, evidencing its importance in the masterful preparations (FERREIRA, 2008; AULTON, 2005).

Therefore, it is necessary to deepen the knowledge about the choice of excipients used in the manipulation of capsules. Thus, given the high consumption of manipulated drugs, as well as the large exposure to excipients, risk of developing adverse effects or even not having an effective treatment, it is important to develop this work in order to ascertain the use of excipients used by magistral pharmacies.

2 METHODOLOGY

2.1 SELECTION OF MASTERFUL PHARMACIES

The study was composed of magistral pharmacies located in cities of the Baixada Fluminense of the State of Rio de Janeiro. The selection was carried out with the help of the Google search site, whose establishments were chosen randomly, obtaining data about the pharmacies such as: commercial name, address, telephone contact and e-mail. Twenty masterful pharmacies were selected.

The contact with the establishments took place in person. Of the twenty pharmacies selected, eleven agreed to participate in the present study.

2.2 DEVELOPMENT OF THE QUESTIONNAIRE

To obtain the data, a questionnaire was developed in the format of a table with multiple alternatives, which was delivered to each of the pharmacies participating in the study. The questionnaire presented space for the completion of the five main drugs in the pharmaceutical form of capsules manipulated in each establishment and a list with different types of excipients used for manipulation of capsules.

2.3 SURVEY OF THE MAIN DRUGS MANIPULATED IN CAPSULE FORM

After collecting data from the master pharmacies participating in the study, a field research was conducted for data collection. Each establishment was visited to obtain authorization to participate in the present study. As authorized, the technical officer provided the data on the main drugs handled in the

establishment. Data were collected between August and February 2020, by completing a questionnaire, in which the pharmacist informed the five main drugs manipulated in the pharmaceutical form of capsules and marked with an X the excipient(s) used for each selected drug.

2.4 STUDY OF THE INTERACTIONS BETWEEN DRUG AND EXCIPIENT

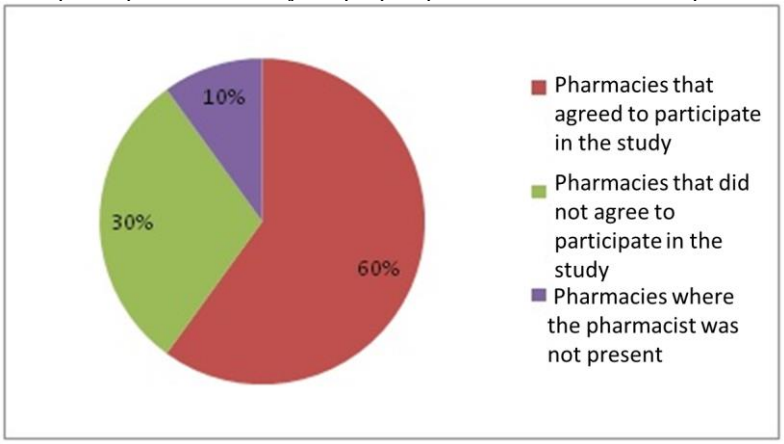
After collecting all the necessary information, a study was conducted to evaluate the possible interactions between drug and excipient, according to the data provided by the selected magistral pharmacies. The study on the correct use of excipients for each was done through bibliographic consultation. This research was based on scientific articles, master's and doctoral dissertations and publications in pharmacy journals, all of which are listed in databases such as SCIELO (Scientific Electronic Library Online), MEDLINE (Medical Literature Analysis and Retrieval System Online), as well as books, official literature such as the Brazilian Pharmacopoeia, package inserts of the referenced drugs and specific monographs of each drug, as provided for in Collegiate Board Resolution No. 67 of October 8, 2007 for the choice of excipients. The following keywords were used for the research: excipient, drug, interaction, masterful and capsules. After that, a determination of the excipients used by the pharmacies evaluated was made to compare the data obtained with the technical-scientific basis.

3 RESULTS AND DISCUSSION

3.1 MAIN DRUGS HANDLED BY THE SELECTED ESTABLISHMENTS

Figure 1 shows the percentage of pharmacies that participated in the study. The sample of results was expressed as a percentage, ranging from 0 to 100 %.

Figure 1: Percentage of pharmacies participating in the study. In red: pharmacies that agreed to participate in the study. In green: pharmacies that did not agree to participate in the study. In purple: pharmacies in which the pharmacist was not present.



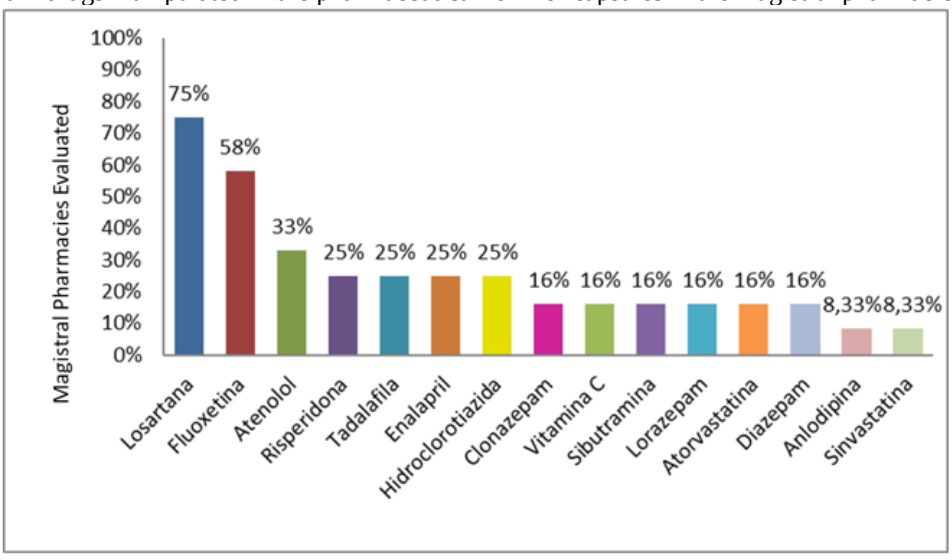
It can be observed that 60% of the establishments agreed to participate in the study, 30% did not accept and 10% did not have the presence of the pharmacist during business hours. In addition to the data presented in percentage, we can highlight one establishment: the pharmacist in charge agreed to list the main drugs manipulated in that place, but refused to answer about which excipients were used for them. Pharmacies that did not participate in the data for some reason were excluded from the data collection.

Of the pharmacies where the pharmacist in charge was not present on site, two were branches, functioning only as prescription collection and drug dispensing stations. According to RDC No. 67, of October 8, 2007, this practice is not allowed, since all pharmacies that have branches must contain fully functioning compounding laboratories in both.

According to Law No. 13,021, of August 8, 2014, the presence of the pharmacist is mandatory during the entire hours of operation of the establishment, ensuring its operation within the scope of pharmaceutical assistance. It is up to the master pharmacist the responsibility to ensure the quality and safety of the products handled (BRAZIL, 2014).

Figure 2 shows the results of the most requested drugs for manipulation in the pharmaceutical form of capsules in the magistral pharmacies evaluated.

Figure 2: Main drugs manipulated in the pharmaceutical form of capsules in the magistral pharmacies evaluated



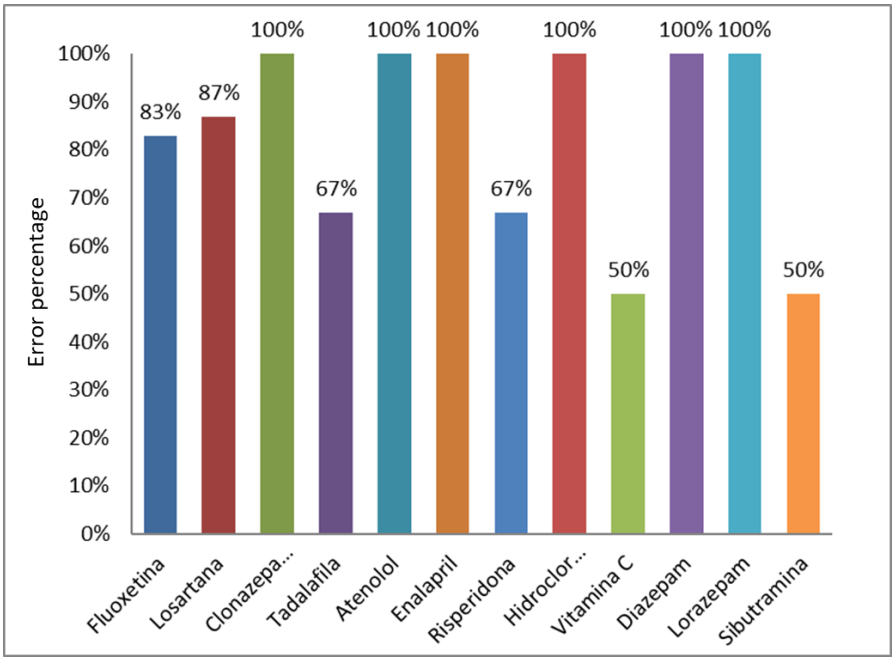
Among the drugs described, we can mention Fluoxetine, Losartan Risperidone, Tadalafil, Atenolol, Enalapril, Clonazepam and Hydrochlorothiazide. Losartan was handled in 75% of the pharmacies, followed by fluoxetine in 58% of the establishments evaluated, followed by Atenolol (33%), Risperidone, Tadalafil, Enalapril and hydrochlorothiazide (25%), clonazepan, vitamin C, sibutramine, lorazepan, artovastatin and diazepan (16%), amlodipine and simvastatin (8.0%).

Among these drugs, four are used for the treatment of arterial hypertension, since this is one of the chronic non-communicable diseases (NCDs) with the highest prevalence of patients, being a worldwide health problem. The drugs are Losartan, Atenolol, Enalapril and Hydrochlorothiazide (ALLEYNE *et al.*, 2013). In addition to these, three drugs are of controlled use, whose action is on the central and peripheral nervous system, such as Fluoxetine which is of the class of antidepressants, Risperidone of the class of atypical antipsychotics and Clonazepam which is a benzodiazepine (Ministry of Health, 2010). Finally, Tadalafil is the drug intended for the treatment of male erectile dysfunction (HARDMAN *et al.*, 2003).

3.2 EVALUATION OF THE EXCIPIENTS USED FOR EACH DRUG

Figure 3 shows the percentage of error of the excipients used for each of the main drugs handled by the selected establishments.

Figure 3: Percentage of error in the choice of excipients for the formulations of the main drugs handled by the pharmacies evaluated



As shown above, Enalapril and Atenolol achieved a 100 % error regarding the choice of excipients. Enalapril belongs to the class of antihypertensive drugs and is considered a prodrug, which through Sodium Enalaprilate, its active metabolite, inhibits the Angiotensin-Converting Enzyme (ECA) (LAURENCE *et AL.*, 2012). For Silva (2006), in the formulation of the drug enalapril it is necessary to add sodium bicarbonate, for the formation of its active form, sodium enalaprilate, through the elevation of pH. This drug can be degraded by hydrolysis when exposed to stomach acidity, requiring an alkalizing buffer agent in the formulations, ensuring its bioavailability (LIMA, 2008). Colloidal silicon dioxide, microcrystalline

cellulose and lactose are examples of excipients compatible with this drug. In addition to these, magnesium stearate can be used as a lubricant and sodium lauryl sulfate 2 % as a surfactant, being used as a wetting agent to not only improve dissolution but also to increase the bioavailability of the drug in question (FERREIRA, 2008; VILLANOVA & SA, 2010).

The main error verified in the formulation of this drug was the absence of sodium bicarbonate as an alkalizing agent, in addition to the non-use of sodium lauryl sulfate in the preparations. This result raises a concern, since Enalapril is a drug of the class of antihypertensive Angiotensin-Converting Enzyme Inhibitors (ACEI) widely used for the treatment of Hypertension (GONTIJO *et al*., 2012).

Atenolol belongs to the class of long-acting cardioselective beta-blockers and is used as the drug of choice in the treatment of cardiovascular diseases (BARNETT *et al*., 2005). According to the Biopharmaceutical Classification System (SCB), this drug is assigned to class III because it has high solubility and low permeability, that is, its permeation through the intestinal membrane is hampered, which leads to a decrease in its bioavailability (FERREIRA, 2008; AMARAL, 2003). As permeability through the biological membrane is a crucial step for the absorption of this drug, it is necessary to introduce a wetting agent in its formulation in order to increase its permeation and consequently increase its absorption and bioavailability (MIRANDA *et al.*, 2013). Among the pharmacies evaluated that handle this drug, both do not use in their formulation a wetting agent, as evidenced by the Figure 3, this being the main factor that led to the 100% error.

The drugs Fluoxetine and Losartan reached an error rate of 83% and 87%, respectively, regarding the choice of excipients. Fluoxetine is a drug of the class of antidepressants Selective Serotonin Reuptake Inhibitors (SSRIs), indicated not only for the treatment of depression, but also to treat Obsessive Compulsive Disorder (OCD), panic disorder, anxiety and post-traumatic disorders (LAURENCE *et al.*, 2012; Pissato et al., 2006). Talc, calcium carbonate and magnesium oxide should not be used in fluoxetine preparations, as drug-excipient interactions may occur, slowing the absorption of this drug. In addition, other excipients can cause problems in its formulation, such as magnesium stearate, which interferes with the dissolution of the drug and consequently its absorption. Lactose is incompatible with fluoxetine, because it reacts with the primary amino group of this drug, through the condensation of the Maillard type, leading to the formation of brownish color products (FERREIRA, 2008). Colloidal silicon dioxide and 20 % microcrystalline cellulose are examples of diluents and absorbents compatible with fluoxetine. Simeticone 1 to 2 % is a lubricant that in addition to being compatible with this antidepressant, also decreases the flatulence caused by this drug, being its main adverse effect (KIBBE, 2000).

The inadequacy of the formulations was regarding the use of pharmaceutical talc in approximately 80% of the pharmacies, in addition to the use of magnesium stearate in 25% of the preparations. As previously described, these excipients should not be used, as they interact negatively with fluoxetine,

impairing its action in the body. A magistral pharmacy used sodium lauryl sulfate as a surfactant, detergent and wetting agent, whose function is to improve the dissolution of drug preparations that have low solubility and difficulty in absorption, but this excipient would not be applied in the manipulation of fluoxetine. According to the SCB, it belongs to class I, thus having high solubility and high permeability, not presenting difficulties in dissolution and absorption in the body (AULTON, 2005). According to Ferreira (2008), wetting agents have the function of increasing the dissolution of drugs and, therefore, have a high influence on their bioavailability. The unnecessary use of this type of excipient should be avoided, as they can alter the bioavailability of drugs, and consequently lead to toxic effects.

Of the pharmacies evaluated, only one used the correct excipient, this generates a great concern, because fluoxetine is a highly prescribed antidepressant, so the correct handling of this drug, as of others, is indispensable (STULZER, 2006).

Losartan belongs to the class of angiotensin II AT1 receptor antagonists, being used in the treatment of arterial hypertension, by inhibiting vasoconstriction and decreasing the production of aldosterone (RANG *et al*., 2011; RIBEIRO & MUSCARÁ, 2001). According to the SCB, this drug is assigned to class III and, therefore, has high solubility and low permeability, thus having a limited absorption, which leads to a low bioavailability (FERREIRA, 2008; FLASH & DALLA, 1999; MIRANDA *et al.*, 2013). In order to increase its permeability and consequently increase its bioavailability, it is necessary that in the formulation of Losartan a wetting agent such as sodium lauryl sulfate is used, thus contributing to improve its dissolution. Being the absence of this in the formulations evaluated, the main cause of error (FERREIRA, 2008; MIRANDA *et al.*, 2013).

The drug Risperidone belongs to the class of atypical antipsychotics, whose action is to block the D2 and 5-HT2 receptors, decreasing the positive and negative symptoms of schizophrenia, in addition to being used in the treatments of psychotic disorder, behavior disorder, autism and obsessive compulsive disorder (OCD) (KOMOSSA *et al*., 2011; MATHEWS & MUZINA, 2007). Starch and sodium lauryl sulfate are chemically compatible with risperidone, but some excipients demonstrate incompatibilities with this drug, they are anhydrous lactose, magnesium stearate and microcrystalline cellulose. Data reveal that such excipients decrease the risperidone content, evidencing chemical incompatibility. In addition, magnesium stearate leads to the formation of degradation products when interacting with the drug (DANIEL, 2013). The error rate obtained in the choice of excipients for risperidone was approximately 67%, and the presence of magnesium stearate and microcrystalline cellulose were the main causes of error in these preparations (Figure 3).

Tadalafil is one of the main drugs used in the treatment of erectile dysfunction, belonging to the class of phosphodiesterase type 5 inhibitors (if5) (FREITAS, 2008). This drug is included in the biopharmaceutical class II, according to the SCB, presenting a high permeability in biological membranes

and low aqueous solubility, which interferes in its dissolution speed and consequently in its absorption (AULTON, 2005). To improve the solubility of Tadalafil it is necessary to introduce excipients in its formulation, with properties of wetting and disintegrating agent, whose objective is to help in the solubilization and absorption of this drug. Sodium lauryl sulfate and sodium starch glycolate are examples of excipients indicated for this purpose (FERREIRA, 2008). Sodium lauryl sulfate is a surfactant that acts by decreasing the surface tension between molecules, favoring the wettability of drugs in water and improving their solubility. Sodium starch glycolate is a disintegrating agent that increases solubility and facilitates the dissolution of drugs (VILLANOVA & SÁ, 2010). As shown in Figure 3, this drug obtained an error of approximately 67%, where the inadequacy of the preparations was due to the non-use of a wetting agent, which is essential for the formula.

Clonazepam is a drug that belongs to the benzodiazepine class, finding itself as one of the most prescribed drugs worldwide. Its action is to inhibit some functions of the central nervous system, being used in the treatments of epilepsy, anxiety and sleep disorders (SHARMA *et al.*, 2010). Clonazepam is insoluble in water and has an absolute bioavailability of approximately 90% (GOODMAN *et al.*, 2012). With these characteristics it falls into the biopharmaceutical class II, according to the SCB, having low solubility and high permeability, having its dissolution speed difficult, this being the factor that restricts the absorption (AULTON, 2005; ALVES, 2017). Thus, it is necessary that in the formulation of this drug contains a wetting and disintegrating agent, in order to increase the solubility of the same and favor its dissolution (MIRANDA *et al.*, 2013). Only one magistral pharmacy provided data on this drug, so it is not possible to obtain conclusive results about the correct choice of excipients for Clonazepam in the establishments under study. However, the only formulation evaluated was inadequate, due to the absence of excipients considered essential to the preparation.

Hydrochlorothiazide is a thiazide diuretic, widely used for the treatment of hypertension. This drug has low solubility in water and its oral bioavailability corresponds to 60 to 80% of the dose, being attributed, according to the SCB, to the biopharmaceutical class II (HARDMAN & LIMBIRD, 2003; BRAZIL, 2010). For drugs belonging to class II it is recommended that in its formulation contain excipients that improve its speed of dissolution, such as wetting and disintegrating agents, providing an increase in solubility and consequently increasing its bioavailability (FERREIRA, 2008; MIRANDA *et al.*, 2013). Like Clonazepam, only one pharmacy provided information about this drug. However, the analyzed formulation was not in accordance with the recommendations, due to the lack of established excipients.

Vitamin C or ascorbic acid presented 50% error in the choice of excipients. Also known as antiscorbutic factor, it is one of the main vitamins, due to the important role it plays in human physiology. (SILVA, 2006). Vitamin C formulations require an antioxidant, because without it, there is a slow reduction of vitamin C, generating a blackening of the mixture. Finally, a diluent such as microcrystalline cellulose or

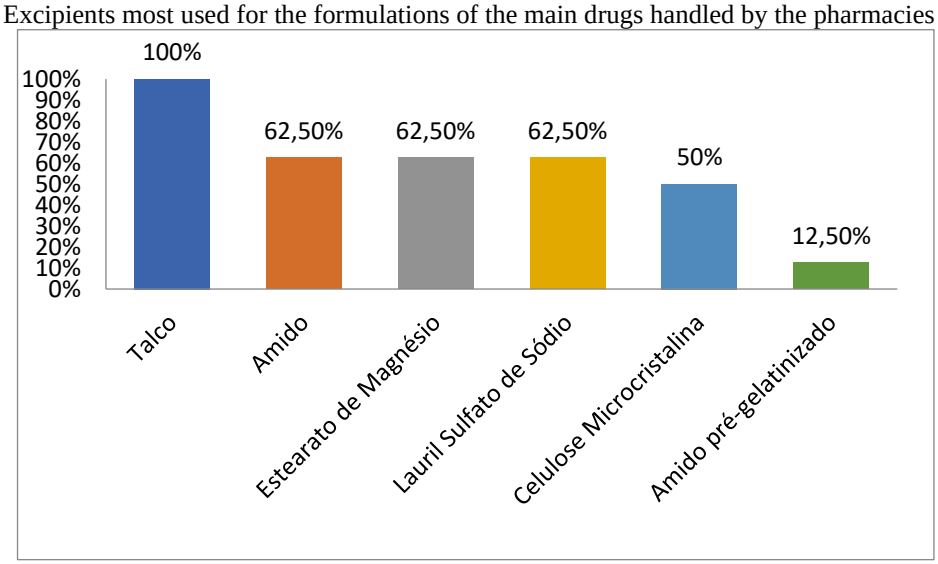
mannitol is added. This vitamin is incompatible with starch, because this excipient is complex with acidic drugs, such as ascorbic acid, which can alter the pharmacological properties of the drug (MATTOS, 2006).

Sibutramine, like vitamin C, also showed a 50% error. It is a drug quickly absorbed by the body, due to these characteristics is a drug that can be classified to class I according to the Biopharmaceutical Classification, presenting high solubility and high permeability, presenting no difficulties as to dissolution and subsequent absorption (Gil & Brandão, 2007; BUCKETT *et al*., 2004; KASIM *et al*., 2004). Thus, it is recommended the use of a diluent and lubricating agent, the most indicated being talc and starch.

3.3 EXCIPIENTS MOST USED IN FORMULATIONS BY SELECTED PHARMACIES

Figure 4 shows the most used excipients for the formulations of the main drugs handled by the establishments evaluated, where the use of talc was highlighted, followed by starch, magnesium stearate, sodium lauryl sulfate, microcrystalline cellulose and finally, pregelatinized starch.

Figure 4: Excipients most used for the formulations of the main drugs handled by the pharmacies evaluated.



The talc was highlighted, reaching the maximum index of 100% of the formulations. This excipient is used as a lubricant in preparations, where its main purpose is to facilitate the flow of powders. Talc is a relatively stable product, but it is incompatible with quaternary ammonium. Its low cost is the main reason for its great use by masterful pharmacies (FERREIRA, 2008; PRISTA, 2003; RAMOS & MOORS, 2013).

The excipients starch, magnesium stearate and sodium lauryl sulfate were used in most formulations, with a percentage of use of 62.5%.

Starch is mainly used as a diluent and has disintegrating and binding action in preparations (GIL & BRANDÃO, 2007). This excipient is widely used by pharmacies because it is stable and does not have

incompatibilities with pharmaceutical products, besides being non-toxic and having a low cost (FERREIRA, 2008; RECIFE, 2013).

Magnesium stearate has lubricating and non-stick action in formulations. Its main limitation of use is that in high concentrations it can delay the dissolution of drugs (PRISTA, 2003).

Sodium lauryl sulfate is used as a wetting and surfactant agent, being widely used for drugs that have a low dissolution rate. Its limitation of use is the incompatibility with lead salts, potassium salts and some alkaloid salts (FERREIRA, 2008; RAMOS & MOORS, 2013).

The two lowest rates of use were microcrystalline cellulose and pregelatinized starch, with a percentage of 50 % and 12.5 %, respectively.

Microcrystalline cellulose can be used as a diluent, disaggregator, adsorbent and lubricant in formulations. It presents stability and compatibility with pharmaceutical actives, but presents incompatibility with oxidizing agents. It has a high cost, which justifies its low use when compared to other excipients, due to its high cost (FERREIRA, 2008; GIL & BRANDÃO, 2007).

Pregelatinized starch is a type of starch modified by physicochemical treatments, being used in formulations as a disintegrating agent, in addition to favoring the speed of dissolution of drugs. Its lower use is due to the fact that its cost is high (PRISTA, 2002; RECIFE, 2013).

As previously presented, the master pharmacist must select the excipients that are compatible with the drug, in order to obtain a safe final product with guaranteed efficacy (ANSEL *et al.*, 2000). The results show that most master pharmacies use in their formulations the excipients of lower cost and do not take into account the possible interactions that they may have with the drug. This practice can compromise the quality of the medication and even harm the patient's health, by causing undesirable effects and / or not having an effective treatment (SCADDING, 2009).

4 CONCLUSION

From the results presented in the present study, it was concluded that there are still large errors in the selection of excipients used in the evaluated formulations of the main manipulated drugs. This fact can impair the quality of pharmaceutical products, compromising their efficacy and safety, as well as bringing consequences to the patient.

It was evident the use of excipients that have lower cost in the preparations, often not being considered the possible interactions of the same with the active ingredient, and it should be emphasized that it is necessary to know the characteristics of each one to ensure the safety, quality and efficacy of the masterful drugs.

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