ARTICLE
https://doi.org/10.22239/2317-269x.01194

Profile of prescription errors of compounding medications in a school pharmacy

Perfil dos erros de prescrições de medicamentos manipulados em uma farmácia-escola

Felipe Cárdia Alves

Márcia Maria Barros dos Passos*

Adriana Silveira Pereira de Melo

Mariana Sato de Souza Bustamante Monteiro

Faculdade de Farmácia, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brasil

* **E-mail:** mmbpassos@gmail.com

Received: Aug 29, 2018
Approved: Dec 17, 2018

ABSTRACT

Introduction: The manipulated medicinal product is a masterly preparation individualized to a patient from a prescription. **Objective:** Evaluate prescriptions at a compounding pharmacy of a federal public university in Rio de Janeiro, and to evaluate compliance of these prescriptions, in relation to the current technical-sanitary criteria. **Method:** This is a descriptive cross-sectional study, which evaluated 400 prescriptions in May 2015. **Results:** About 162 (40.00%) prescriptions presented errors, of which 132 showed exclusively bookkeeping errors, 20 exclusively, pharmacotechnical errors, and 10 both errors. Among the errors in bookkeeping, the most frequent were absence of date of issue (29%) and posology (13.00%). Among the pharmacotechnical errors, 66.33% were incompatibility between the active and formulation, 13.33% were incompatibilities between different active in the same formulation and 23.33% were incompatibilities of the active with the semi-solid vehicle. Therefore, it was possible to identify that the prescriptions analyzed did not adequately comply with the Brazilian legislation, as errors were verified in both bookkeeping and pharmacotechnical aspects. **Conclusions:** Because they are manipulated drugs, which must be developed through a prescription, it is essential to carefully evaluate them to minimize or avoid damages to users.

KEYWORDS: Drugs Prescription; Pharmaceutical Compounding; Pharmacoepidemiology

RESUMO

Introdução: O medicamento manipulado é uma preparação magistral individualizada a um paciente a partir de uma prescrição. **Objetivo:** Avaliar as prescrições atendidas em uma farmácia com manipulação de uma universidade pública federal no Rio de Janeiro e avaliar o cumprimento destas prescrições, em relação aos critérios técnico-sanitários vigentes. **Método:** Estudo transversal descritivo no período do mês de maio de 2015, que avaliou 400 prescrições atendidas no período. **Resultados:** Cerca de 162 (40,00%) prescrições apresentaram erros, das quais 132 prescrições mostraram, exclusivamente, erros de escrituração, 20 exclusivamente erros farmacotécnicos e 10 ambos os erros. Dentre os erros de escrituração, os mais frequentes foram ausência de data de emissão (29,00%) e posologia (13,00%). Entre os erros farmacotécnicos, 66,33% foram de incompatibilidade entre o ativo e formulação, 13,33% foram incompatibilidades entre diferentes ativos de uma mesma formulação e 23,33% foram incompatibilidades do ativo com a base semissólida prescrita. Portanto, foi possível identificar que as prescrições analisadas não atenderam adequadamente ao estabelecido na legislação brasileira, pois verificou-se erros tanto dos aspectos da escrituração quanto farmacotécnico. **Conclusões:** Por se tratarem de medicamentos magistrais, os quais devem ser desenvolvidos mediante uma prescrição, torna-se fundamental a avaliação criteriosa para minimizar ou evitar danos aos usuários.

PALAVRAS-CHAVE: Prescrição de Medicamentos; Farmácia com Manipulação; Farmacoepidemiologia

INTRODUCTION

A compounding medication is any drug produced after compounding the formula contained in a medical prescription[1]. Compounding is a set of pharmacotechnical operations with the purpose of elaborating magistral, officinal preparations and fractioning pharmaceutical specialties for human use[1]. A magistral preparation is prepared in the pharmacy, based on a prescription from a qualified professional, aimed at an individual patient, and which sets out in detail its composition, pharmaceutical form, dosage and mode of use. An officinal preparation is that prepared in the pharmacy and whose formula is registered in the National Form or International Forms recognized by the Brazilian National Health Surveillance Agency (Anvisa)[1].

A compounding or magistral pharmacy is the establishment where magistral and officinal formulas are developed. They also market drugs, medicines, pharmaceutical supplies and related products, serving hospital units or any other equivalent healthcare unit[2].

These currently account for a significant share of the Brazilian drug market. This sector built momentum in Brazil in the late 1980s and has had steady growth. Although today the number of these establishments is stable, Brazil has about 7,000 registered compounding pharmacies.

The increase in the number of compounding medicines in Brazil resulted in greater concern about the quality of these products. For this reason, Anvisa published, on April 19, 2000, the first specific regulation for this sector, the Resolution of the Collegiate Board (RDC) n. 33, which set forth good compounding practices and improved the quality of compounded products[3]. Ever since this publication there has been a steady update movement. The current RDC is n. 67, of October 8, 2007, supplemented by RDC n. 87, of November 21, 2008.

According to Rowa et al.[4], pharmaceutical compounding is the combination, mixing or modification of substances to provide a custom-made drug to a patient as required by the prescriber. Generally, the compounding process is used because of its versatility and flexibility to obtain a new drug that does not exist in the pharmaceutical market, such as: modification of the dose of the active ingredient, or combination of several active ingredients, or modification of the pharmaceutical form, or change of the type of excipient[4], or to customize patient therapy with unique patient-specific compounding drugs[5]. Compounding drugs value the prescribing physician, improve the doctor-patient relationship and enable adjusting the formula to the patient, who, as a single and individual person in his or her symptoms, does not always adapt to commercially available formulations[6,7].

According to Bonfilio et al.[3], compounding requires careful selection of the active ingredients, fillers and adjuvants, as well as an assessment of their content, to achieve the desired therapeutic efficacy, once the pharmacist is responsible for both the preparation and evaluation of prescriptions and risks involved in the compounding process due to uncertainty about drug bioavailability and drug stability[8].

In this context, prescriptions are potential sources of error, since compounding drugs are different from those available on the market.

In addition, overall, prescription errors are highly prevalent. Countless studies indicate a wide range of prevalence ranging from 8% to 56%[9,10,11,12,13,14]. In Brazil, many studies indicate prescription errors of various types, which ranged from 12% to 91.75%, and included errors like ineligibility, lack of description of the drug and its use, as well as lack of information about the user and the prescriber. This type of error endangers patient therapy both in outpatient settings[15,11,12,13,14]and in hospital settings[9,10,16]. However, studies about prescription errors in compounding settings have not been found.

According to Dean et al.[17], prescription errors can be divided into two groups. The first refers to decision-making errors, like prescribing a medication that is contraindicated to that patient, or to an allergic patient, or prescribing drugs at a lower or higher dose. The second group refers to errors involved in the write-up work of the prescription containing essential information mistakes that include: writing illegibly, writing a drug name in abbreviated form or using non-standard nomenclature, omitting the prescriber's signature, omitting the administration route and prescription transcription mistakes. According to Dalal et al.[18], prescription errors may include the wrong drug, dosage, amount, route of administration, duration of treatment, number of doses, drug concentration, and even readability.

In addition to the errors described, prescriptions of compounding drugs may also contain errors of chemical incompatibility and pharmacotechnical unfeasibility, since this act is expressed through a pharmaceutical formulation, whose adjuvants may interact in the formulation and cause problems of chemical and physical incompatibility or hinder the delivery of a given drug in the prescribed pharmaceutical form[7].

In Brazil, Good Practices for the Compounding of Magistral and Officinal Preparations for Human Use in pharmacies include pharmaceutical prescription assessment as one of the steps of the process[1]. This assessment includes checking and analyzing the prescription and weighing form or compounding order. In the prescription, the concentration and physicochemical compatibility of the components, dose and route of administration, pharmaceutical form and degree of risk should be assessed. The prescription must be properly stamped, with the pharmacy record and date of compounding and the weighing form or compounding order must be stamped and signed by the responsible technician.

Thus, the analysis of prescriptions is an essential step to reveal possible failures that may impair the treatment and

the patient's health. It is an activity that deserves attention and importance in the pharmaceutical sector. However, there are still few studies regarding the analysis of prescriptions in the compounding sector, which makes studies in this area even more relevant.

The present study aims to identify the quality of prescriptions of compounding drugs done in a compounding pharmacy of a Brazilian public university, regarding aspects of write-up work and pharmacotechnical feasibility.

METHOD

This is a descriptive cross-sectional study on medication use, conducted to investigate the quality of prescriptions for compounding medications that were done at a school pharmacy. Its location is a public university in the city of Rio de Janeiro, Brazil, which serves an average 300 patients/day, mainly from the Unified Health System (SUS), but also from private clinics.

During May 2015, about 400 prescriptions of compounding drugs were done during this period and selected to be the sample of this study. Based on the prescriptions, a spreadsheet on Microsoft Excel® with the registration of the study variables arranged in two groups was prepared:

Variables describing errors in write-up work: including the mandatory requirements that must be present in a prescription, according to the health regulations in force[1], such as: be written in ink; be readable; have the prescriber's name; signature and registration number on the professional association; prescriber's office or home address; patient's name; issue date; drug formulation; dosage; route of administration; pharmaceutical form and dosage.

Variables describing pharmacotechnical errors: for a more detailed analysis of errors arising from problems in pharmacotechnics, three variables were created based on the following parameters: compatibility between active ingredient and formulation; compatibility between active ingredients in the same formulation and compatibility of the formulation with the prescribed semi-solid vehicle.

Compatibility errors between active ingredients and the formulation were defined as those in which formulations were unable to incorporate the active ingredient due to chemical or physical interaction between them. Active ingredient compatibility errors refer to the chemical incompatibility between active ingredients of a given formulation. Formulation compatibility errors correspond to the impossibility of incorporating the active components in a given pharmaceutical form.

The evaluated variables were sorted into the following categories: presence of prescription error (yes/no); type of error (write-up work or pharmacotechnical); number of errors per prescription; medicine involved in the error. Then, the data were analyzed on Microsoft Excel® and presented as absolute and relative frequencies in tables.

The study was approved by the Research Ethics Committee involving Human Beings of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro (HUCFF-UFRJ), under opinion n. 1.636.337.

RESULTS

This study included 400 prescriptions, which presented at least one magistral or officinal formulation. Among these, 162 prescriptions had errors: 132 had only write-up errors, 20 had only pharmacotechnical errors and 10 prescriptions had both types of errors. Table 1 shows the absolute and relative frequency of information obtained from prescriptions, regarding errors in write-up and pharmacotechnics.

When it comes to the number of errors per prescription, 122 prescriptions had one error, 33 prescriptions had two errors, five prescriptions had three errors and two prescriptions had four errors, totaling 211 errors, with an average of 1.3 error per prescription.

Of the 30 prescriptions that had pharmacotechnical errors, 19 prescriptions (63.30%) were related to the incompatibility of the active ingredient with the formulation, seven prescriptions

Table 1. Frequency of error descriptors present in prescriptions evaluated in the period of May 2015 in a compounding pharmacy of Rio de Janeiro.

Error descriptors	N	%
Write-up work		
Written in ink or typed	3	1.40%
Readability	11	5.2%
Patient's name	0	0.00%
Concentration	17	8.00%
Official nomenclature	10	4.80%
Pharmaceutical form	24	11.40%
Dosage	26	12.30%
Issue date	60	28.40%
Prescriber's name	6	2.80%
Office or home address	17	8.00%
Registration of the professional in the trade association	7	3.30%
Pharmacotechnicals		
Incompatibility between formulation and active ingredient	19	9.00%
Incompatibility between active ingredients in the same formulation	4	1.90%
Incompatibility of active ingredients with prescribed base	7	3.40%
Total	**211**	**100.00%**

Table 2. Frequency of active substances according to the types of errors present in the prescriptions evaluated in the period of May 2015 in a compounding pharmacy of Rio de Janeiro.

Incompatibility/Substance	N	
Between the active ingredient and the formulation		
Phytic Acid, Glycolic Acid (Lanette Cream)	1	
Glycolic Acid, Hydroquinone, Phytic Acid, Kojic Acid, Hydrocortisone, Alpha Bisabolol (Cream)	1	
Hydroquinone, Phytic Acid, Kojic Acid (Lanette Cream)	1	
LCD, salicylic acid (solid Petroleum jelly)	2	
LCD, salicylic acid, allantoin (diadermin)	2	
LCD, salicylic acid, allantoin (solid petroleum jelly)	8	
Urea, Salicylic Acid, PCA-Na (Lanette Cream)	2	
Urea, Ammonium Lactate, SAO (Lanette Lotion)	1	
Urea Salicylic Acid (Diadermin)	1	
Subtotal		19
Among Assets of the Same Formulation		
Salicylic acid, Urea, Ketoconazole, SAO, GSO, Desonide (Cream)	2	
Ketoconazole, Salicylic Acid, Silicone, Urea (missing formulation)	1	
Urea, Ketoconazole (Cream)	1	
Subtotal		4
Between formulation and base		
Calamine, Marigold, SAO, GSO (Lanette Cream)	1	
Potassium Chloride (Syrup)	1	
Urea, Salicylic Acid, SAO, GSO, Allantoin (Lanette Cream)	1	
Urea, Salicylic Acid, PCA-Na (Lanette Cream)	1	
Urea, SAO, GSO, marigold (Lanette Cream)	1	
Urea, SAO, GSO (Lanette Lotion)	1	
Urea, Mineral Oil (Lanette Cream)	1	
Subtotal		7

LCD: *liquor carbonis detergens*; PCA-Na: sodium pyrrolidone carboxylate; SAO: sweet almond oil; GSO: Grape Seed Oil.

(23.33%) were related to the incompatibility of the active ingredient with the semi-solid vehicle and four prescriptions (13.33%) presented incompatibility between the active ingredients. The main active ingredients involved in pharmacotechnical errors are described in Table 2. The pharmaceutical formulation that most presented pharmacotechnical incompatibility and appeared more frequently in the prescriptions has the active ingredients of *liquor carbonis detergens* (LCD), salicylic acid and allantoin in solid petroleum jelly.

Table 3 presents the pharmaceutical formulations that had errors in relation to the prescribed pharmaceutical form. Solid petroleum jelly ointment and Lanette cream had the highest number of errors.

Table 3. Frequency of pharmaceutical forms related to errors found in prescriptions evaluated in the period of May 2015 in a compounding pharmacy of Rio de Janeiro.

Pharmaceutical form	N	(%)
Ointment (solid petroleum jelly)	10	33.33%
Lanette Cream	9	33.00%
Base cream	4	13.33%
Diadermin Cream	3	10.00%
Lanette Lotion	2	6,67%
Syrup	1	3.33%
Other pharmaceutical form	1	3.33%

DISCUSSION

The results indicated a frequency of 40.50% errors and an average of 1.3 error per prescription. Prescription errors are characterized by preventable events that result in inappropriate use of the drug with or without harm to the patient. Reed-Kane et al.[19] verified, in a compounding pharmacy, the occurrence of errors in electronic prescriptions of about 3%, and the most common error was the wrong insertion of the medication in the electronic form.

In an outpatient pharmacy, there was a frequency of 1.9 error/prescription[20]; and in a hospital pharmacy, 3.3 errors/prescription[21]. The discrepancy of these results is probably due to the presence of a higher number of manufactured drugs in prescriptions filled at the outpatient pharmacy. Furthermore, according to Shipra et al.[22], the greater the number of prescription drugs, the greater the likelihood of prescription errors.

Prescriptions evaluated at the school pharmacy had a relatively low error rate per prescription: 1.3 error/prescription. This fact can be attributed to the origin of most prescriptions: a school hospital. One of the strategies to improve the quality of prescriptions is to encourage the contact between pharmacists and prescribers to inform the verified nonconformities and possible resolutions of the irregularities found in the prescriptions. However, it should be considered that the prescribing professional is not always present or accessible full-time, with availability to return the pharmacist's contact by phone, mainly because of their work schedules.

Of the errors in write-up work, the most frequent were: the date of issue of the prescription or its absence (28.4%), followed by the dosage (12.3%), pharmaceutical form of the drug (11.4%), and concentration of active ingredients (8%). The only item that showed no errors was the patient's name, which was present in all prescriptions. The other errors were observed with relatively low frequency.

However, regardless of its magnitude, health information about the drug, like concentration, pharmaceutical form, official nomenclature and dosage are important in a prescription, since their absence can cause lethal errors for the patient, as well

as waste and ineffectiveness of drug therapy. However, this study found a low rate when compared to other studies[11,12,13]: which presented a total error of 70% for absence of concentration data, 22% for absence of pharmaceutical form and 57% for absence of dosage.

The dosage was the only item in which the rate was similar to that of other studies, requiring greater attention to this item, since it is extremely important for efficacy and safety in drug therapies. However, errors must be avoided to ensure patient health.

The descriptors related to the physicians, like name, registration in the Regional Medical Council (CRM) and office address, are essential pieces of information, which may be related to falsification and fraud of prescriptions and contribute to the illegal and/or abusive use of drugs[11]. Noto et al.[23] identified prescriptions from physicians who were not on the list of the council of the state where they worked. Among these there were several doctors from other states and some foreigners who were not licensed to work, like physicians who had been banned from the profession by the CRM and even some who had died a year earlier. Studies by Mastroianni[11], Valadão et al.[12] and Guzatto and Bueno[13] have also shown high rates in relation to medical descriptors, such as the absence of the physician's name and CRM, with an average error frequency of 25.33% and 15%, respectively. This result was higher than the errors found in the present study, which were 2.8% and 3.3%, respectively. These situations may also indirectly interfere with the patient's health condition, considering that unauthorized professionals may damage the patient's health by performing an unauthorized function.

Readability of the actual writing and the date of the prescription are also important information for the patient's orientation, since, in the case of illegibility, this can compromise the communication between physicians and pharmacists. This can lead to the wrong dispensation of the patient's medication and the patient's misunderstanding of the therapy. Moreover, some prescriptions were written in pencil, and this type of error can cause the prescription to be tampered with by the patient or by third parties, which can also cause health problems. The frequencies of readability errors found in the studies by Mastroianni[11] and Guzatto and Bueno[13] resulted in an average of 67% of errors, which was higher than that found in this study (5.7%).

Errors regarding the date of issue of the prescription have shown a frequency of 15%. Although not justifiable, they may occur due to the request of patients to physicians. Some patients want to have more than one prescription to avoid paying for a new appointment, mainly driven by lack of money. However, the possibility of forgetfulness of the prescribing professional cannot be ruled out. This percentage (15%) is low compared to other studies[11,12,13], which have shown a frequency of approximately 30% of these errors. This shows that prescriptions that arrive at the pharmacy-school have, in general, a smaller amount of errors, and this shows some degree of commitment to the quality of prescriptions due to the constant presence of a pharmacist in the dispensing sector. Furthermore, it is a school hospital, which puts particular emphasis on proper professional training.

Regarding pharmacotechnical errors, compatibility errors between active ingredients and formulations stood out with 63.33% of frequency, while errors in the feasibility of the formulation, which represents the compatibility of the active ingredient with the prescribed base, presented a frequency of 23.33%, and errors regarding compatibility between different active ingredients in the same formulation presented a frequency of 13.33%.

Although compatibility errors between the active ingredients with the formulation were more frequent, these can be fixed by the pharmacist's performance and knowledge, which enable them to ensure the feasibility and production of the drug, through changes in the formulation. Thus, its high frequency in relation to other errors can be attributed to the training of prescribing professionals, which does not include drug preparation, compounding techniques, doses, pharmaceutical forms and physicochemical interactions between active ingredients, excipients and vehicle.

When it comes to the feasibility of the formulation with the prescribed vehicle, these errors usually occur due to specification of the semi-solid vehicle by the prescribing professional, such as Lanette cream, which is prescribed as a vehicle for formulations containing high concentrations of urea, oils, liquid active ingredients and acids. Creams are emulsions that consist of a two-phase system with at least two immiscible liquids, in which one of the liquids is dispersed as small drops (internal or dispersed phase) into the other liquid (external or continuous phase). It is usually stabilized by one or more emulsifying agents[24]. The presence of an emulsifying agent is essential for stabilizing the formulation; these are surfactants that have two distinct parts: one hydrophilic and one lipophilic[25], and the relationship between these parts in the surfactant molecule is measured by the hydrophilic-lipophilic balance (HLB). The surfactant HLB must be equal to the HLB of the oily emulsion components to produce a stable system. In addition, there are nonionic surfactants, which have no charge on the hydrophilic part, and ionic surfactants, which ionize in aqueous solution, providing cations or anions[26].

Consequently, maintaining the HLB is essential to ensure the incorporation of the desired active ingredients into the emulsion. That's because an emulsion with a certain oil phase proportion requires a surfactant with a certain HLB. When that phase has its proportion changed, this surfactant can no longer stabilize the emulsion. Another parameter that influences emulsion stability is the presence of oppositely charged active ingredients or a high concentration of ionically surfactant-like active ingredients, which can lead to emulsion incompatibility and destabilization. Therefore, some active ingredients can only be delivered in Lanette cream in low concentrations.

Lanette cream is an anionic cream, since it has a negatively charged surfactant in its composition. Therefore, high concentrations of certain active ingredients can destabilize this base, requiring the use of another base. Some prescribing professionals make these mistakes when defining the type of base that will be the vehicle of the active ingredients. In this situation a prescription without specification of the base to be used would be feasible, leaving it to the pharmacist to use the most appropriate base, since once Lanette cream, rather than base cream, is prescribed, the formulation is subject to the characteristics of the specified cream, leading to feasibility and incompatibility errors, depending on the formulation. The same applies to ointments, which are prescribed as solid petroleum jelly, whereas, once prescribed as a base ointment, the pharmacist would be responsible for using the most appropriate ointment, thus avoiding prescription errors.

Compatibility errors between different active ingredients are even more specific than the others, occurring in particular cases, which justifies their lower frequency in relation to others. In this context, 19 drugs involved with this type of error were found. The main problem observed was the use of solid petroleum jelly as a vehicle for LCD and salicylic acid. LCD is a preparation made from standardized keel dye coaltar extracts containing benzene, naphthalene, phenols, small amounts of pyridine and quinoline, which are compounds with polar or hydrophilic characteristics. Solid petroleum jelly is an extremely lipophilic or nonpolar base and is therefore incompatible with LCD, hindering the incorporation and homogenization of the active ingredient in this base. It is necessary to prepare this medication in another vehicle, like a base ointment, which is a mixture of solid petroleum jelly with lanolin in the ratio of 7:3[24]. Lanolin has amphiphilic characteristics, thus this molecule has hydrophilic and hydrophobic regions[25], which allows the incorporation of the alcoholic extract.

Another observed incompatibility occurred with diadermine cream as a vehicle for LCD, salicylic acid and urea. In this case, diadermin cream is an oil-in-water emulsion containing stearic acid in concentrations ranging from 15% to 25%, which is partially saponified. Saponification is made with emulsifying alkaline agents like sodium or potassium hydroxides or carbonates, dilute ammonia solution, triethanolamine, 95% aminomethylpropanol (AMP) or sodium borate[24]. Thus, this base has sensitivity to the incorporation of acid active ingredients that destabilize the emulsion, because the acid neutralizes the alkaline emulsifying agent, responsible for keeping the formulation stable, leading to viscosity loss and emulsion separation, making the formulation unfeasible.

In addition, urea has hygroscopic characteristics and is very water soluble. It is, therefore, solubilized in the aqueous part of the emulsion, reducing the proportion between the oily and aqueous phases, destabilizing it.

Other situations of base incompatibility of the active ingredient occurred with urea, salicylic acid, sodium pyrrolidone carboxylate (PCA) in Lanette cream; urea, ammonium lactate, sweet almond oil (SAO) in Lanette lotion; and phytic acid and glycolic acid in Lanette cream. In all cases, it is possible to notice the presence of acids in the formulations, which generates an incompatibility with the Lanette base, since, as previously mentioned, this base is an oil-in-water emulsion with anionic surfactant. Anionic surfactants have functional groups that, when ionized in aqueous solution, provide negatively charged organic ions that interact with acid active ingredients, which are negatively charged[26,27].

In the case of ammonium lactate and PCA-Na, regardless of their concentrations, the cream is destabilized, because ammonium lactate corresponds to the ammoniacal salt form of lactic acid and PCA-Na is a sodium salt of pyrrolidone carboxylic acid, and ionizes in aqueous solution, and interacts with the anionic surfactant that forms Lanette cream. In the case of acids, the prescribed concentrations were high, above 10%, as well as the concentration of urea, above 30%, and therefore they destabilized the Lanette cream.

Although it is a standardized preparation described in the pharmacopoeia, Lanette cream may have a variation in its composition, according to the pharmacy in which it is produced, and this may interfere with its resistance to the incorporation of active ingredients. In the pharmacy-school where this study was conducted, Lanette cream has 10% oily phase and does not support the incorporation of high levels of active ingredients, like the acids mentioned and with ammonium lactate and PCA-Na, because the base has its charges neutralized, destabilizing the emulsion. Therefore, in this study, the incorporation of Lanette-based charged active ingredients can be considered as an incompatibility. An alternative for incorporating high levels of charged active ingredients is the use of nonionic cream, whose surfactant, which compose this base, has no charge.

It was also possible to verify formulations of glycolic acid, hydroquinone, phytic acid, kojic acid and hydrocortisone in Lanette cream. As already mentioned, acids are not compatible with Lanette cream and in this case the base to be used should be nonionic cream. However, hydroquinone is not compatible with this cream and should therefore be incorporated into Lanette cream. This result of incompatibility between hydroquinone and nonionic cream is seen in practice, but there are no studies to explain the fact. It is known, however, that hydroquinone is easily oxidized[28] and, therefore, may undergo an oxidation process along with nonionic cream due to its composition, which can lead to destabilization of the cream. In this case, two independent formulations should be compounded to meet the therapeutic demand of the patient. Nevertheless, this procedure may lead to difficulty in adhering to the treatment, because it is necessary to apply two creams to the same place, making the administration of the drug more inaccurate.

Regarding incompatibilities between active ingredients in the same formulation, a total of four errors were observed, all involving ketoconazole and urea. These formulations were defined as incompatibility between active ingredients due to patient

complaints about the yellowish color of the drug. Because of this, the pharmacy school does not produce any medicine that associates these two components.

Although no such chemical incompatibility has been found in the literature, no mention was made of this color change observed in practice. However, in this study it was chosen to classify this observation as an incompatibility between active ingredients, since there may be the interaction, characterized by color change, which may be related to the decay of the active content or formation of other compounds as described by Mendonça et al.[29]. Ketoconazole alone is usually pink, but when associated with urea it had another color.

In this case, different situations may contribute to color change, external factors like temperature, light or interactions between molecules, since ketoconazole is an easily oxidized and photosensitive drug[29,30], sensitive to the conditions described. However, for a more accurate explanation, more detailed studies with analytical experiments are necessary to determine what happened.

In the feasibility analysis of the formulation with the prescribed base, there were seven cases in which it was not feasible to perform the formulation according to the prescription, due to high concentration of active ingredient, large amount of oils and the inability to solubilize the drug in the formulation. The cases are: 10% potassium chloride in syrup, which was prescribed at a higher concentration than usual and, at this concentration, the active ingredient does not solubilize, resulting in syrup with part of the insoluble active ingredient, which does not allow the homogenization of the formulation and may cause variation of the administered dose, compromising the drug action.

Syrup is a sugar- and water-based pharmaceutical form in which sugar is close to saturation concentration, so the amount of free water to solubilize potassium chloride is low, which makes the formulation unable to solubilize high amounts of salt. The usual concentration at which syrup should be made is 6%, the threshold on which potassium chloride solubilizes in syrup, as described in the Brazilian Pharmacopoeia National Form[24].

Another case was the prescription of urea, salicylic acid, clobetasol in Lanette cream, which contained a high concentration of urea (30%) and salicylic acid (15%). As explained above, high concentrations of salicylic acid and urea destabilize Lanette cream, rendering the incorporation of active ingredients[30].

Drugs containing urea, grape seed oil (GSO), sweet almond oil (SAO) and marigold in Lanette cream or the same previous formulation adding allantoin and/or marigold were also incompatible with Lanette cream. Since Lanette cream produced in the school pharmacy has 10% oily phase, when a high concentration of oil is incorporated into this emulsion, there is an increase in the oily phase of this system, changing its HLB. However, by increasing the amount of one of the emulsion phases, either aqueous or oily, the surfactant that was present at a certain concentration with a certain HLB value will no longer be able to stabilize the system, causing greater resistance to the incorporation of oily components and forming an immiscible system again[30]. This phenomenon can occur in formulations in which a total concentration of oils and other liquid active ingredients above 25% will be incorporated, which completely destabilizes Lanette cream.

The dosage forms that most presented prescription errors were ointment and cream, with a frequency of 33.33% and 30%, respectively. However, these dosage forms were the most prescribed, which justifies their higher rate of errors. In both cases these errors could be avoided by prescriptions that did not specify the semi-solid vehicle to be used, leaving it at the pharmacist's selection to use the most appropriate base as previously described.

The same situation occurred with diadermine cream and Lanette lotion, which were directly involved in the error due to the specification of the base.

In the cases of syrup and base cream, the errors found were not the result of prescriptions that specified the bases, but errors related to the characteristics of the active components of the formulation.

CONCLUSIONS

It can be identified that the prescriptions analyzed do not yet meet the requirements of Brazilian law. Both write-up and pharmacotechnical aspects showed errors. Because these are compounding drugs, the situation is even worse due to errors inherent in the formulations, given the possibility of delivering the active ingredients in different concentrations, vehicles and pharmaceutical forms to enable a customized or adapted formulation, making careful evaluation key to minimize or prevent harm to users.

It is necessary to implement strategies aimed at the correct filling of prescription drugs, in order to reduce possible medication errors. An alternative would be the professionals' understanding of the importance of correct prescriptions and the need for an education process that makes prescribers aware of the pharmacotechnical aspects of the formulation so that such errors are prevented. Because of the performance of the pharmacist, in the latter case errors can be minimized, but still, the risk remains. However, the joint action of professionals, pharmacists and physicians can ensure greater prescription safety, thus ensuring patient therapy too. For this it is important that there is communication and mutual respect between both professionals to guarantee the quality and safety of the drug therapy.

Most of the prescriptions evaluated came from a university hospital, so they do not necessarily reflect the quality of the entire compounding industry, since errors are expected to be minor in a public school hospital of this type.

This study is also important to generate further information about the compounding industry. This information can contribute to reveal the reality of patient safety and show there is still much room for research that evaluates the quality and efficacy of compounding drugs.

Finally, prescription errors are preventable. In this sense, failures in the process of compounding and use arising from the prescription of medications are considered important factors that, if prevented, will contribute to patient safety.

REFERENCES

1. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução RDC Nº 67, de 8 de outubro de 2007. Regulamento técnico sobre boas práticas de manipulação de preparações magistrais e oficinais para uso humano em farmácia e seus anexos. Diário Oficial União. 9 out 2007.
2. Brasil. Lei Nº 13.021, de 8 de agosto de 2014. Dispõe sobre o exercício e a fiscalização das atividades farmacêuticas. Diário Oficial União. 9 ago 2014.
3. Bonfilio R, Emerick GL, Netto Júnior A, Salgado HRN. Farmácia magistral: sua importância e seu perfil de qualidade. Rev Baiana Saude Publ. 2010;34(3):653-64. https://doi.org/10.22278/2318-2660.2010.v34.n3.a63
4. Rowa ANZ, Al-Ramahib, Shahedc Q, Salehc B, Elarajb J. Determinants and frequency of pharmaceutical compounding in pharmacy practice in Palestine. Int J Pharm Practice. 2011;20(1):9-14. https://doi.org/10.1111/j.2042-7174.2011.00157.x
5. Treadway AK, Craddock D, Leff R. Practices of pharmacies that compound extemporaneous formulations. Am J Health Syst Pharm. 2007;64(13):1403-9. https://doi.org/10.2146/ajhp060251
6. Ribeiro AMRF. Análise da prescrição de manipulados farmacêuticos na região do Porto [dissertação]. Porto: Universidade Fernando Pessoa; 2014.
7. Miguel MD, Zanin SMW, Miguel OG, Roze AO, Oyakawa CN, Oliveira ABO. Cotidiano das farmácias de manipulação. Visao Acad. 2002;3(2):103-8.
8. Fois RA. Compounded medicines and “off label” prescribing: a case for more guidance. Aust Farm Physician. 2009;30(1/2):16-20.
9. Alanazi MA, Tully MP, Lewis PJ. A systematic review of the prevalence and incidence of prescribing errors with high-risk medicines in hospitals. J Clin Pharm Ther. 2016;41(3):239-45. https://doi.org/10.1111/jcpt.12389
10. Ashcroft DM, Lewis PJ, Tully MP, Farragher TM, Taylor D, Wass V et al. Prevalence, nature, severity and risk factors for prescribing errors in hospital inpatients: prospective study in 20 UK hospitals. Drug Saf. 2015;38(9):833-43. https://doi.org/10.1007/s40264-015-0320-x
11. Mastroiani PC. Análise dos aspectos legais das prescrições de medicamentos. Rev Cienc Farm Basica Apl. 2009;30(2):173-6.
12. Valadão AF, Firmino KF, Moreira ALP, Gastro GD, Loures GF, Públio RN et al. Estudo das prescrições de medicamentos nas unidades básicas de saúde de Coronel Fabriciano – MG, quanto aos preceitos legais. Rev Bras Farm. 2008;89(4):298-301.
13. Guzatto P, Bueno D. Análise de prescrições medicamentosas dispensadas na farmácia de uma unidade básica de saúde de Porto Alegre – RS. Rev HCPA. 2007;27(3):20-6.
14. Aguiar G, Silva Junior LA, Ferreira MAM. Ilegibilidade e ausência de informação nas prescrições médicas: fatores de risco relacionados a erros de medicação. Rev Bras Prom Saude. 2006;19(2):84-91. https://doi.org/10.5020/18061230.2006.p84
15. Valadão AF, Moreira ALP, Andrade LC, Pires CA, Firmino KF, Brum CA. Prescrição médica: um foco nos erros de prescrição. Rev Bras Farm. 2009;90(4):340-3.
16. Anacleto TA, Perini E, Rosa MB, César CC. Drug-dispensing errors in the hospital pharmacy. Clinics. 2007;62(3):243-50. https://doi.org/10.1590/S1807-59322007000300007
17. Dean B, Schachter M, Vincent C, Barber N. Causes of prescribing errors in hospital inpatients: a prospective study. Lancet. 2002;359(9315):1373-8. https://doi.org/10.1016/S0140-6736(02)08350-2
18. Dalal K, Barto D, Smith T. Preventing medication errors in critical care. Nurs Crit Care. 2015;10(5):27-32. https://doi.org/10.1097/01.CCN.0000471002.71461.8d
19. Reed-Kane D, Vasquez K, Pavlik A, Peragine J, Sandberg M. E-prescription errors and their resolution in a community compounding pharmacy. Int J Pharm Compd. 2014;18(2):159-61
20. Frick GGG, Bonotto LF, Bernardi CLB, Pletsch UM. Principais problemas encontrados nas prescrições em um município da região noroeste do estado do Rio Grande do Sul. Rev Contexto Saude. 2010;10(19):108-11. https://doi.org/10.21527/2176-7114.2010.19.108-111
21. Rosa MB, Perini E, Anacleto TA, Neiva HM, Bogutchi T. Erros na prescrição hospitalar de medicamentos potencialmente perigosos. Rev Saude Publ. 2009;43(3):490-8. https://doi.org/10.1590/S0034-89102009005000028
22. Shipra J, Prerna U, Jaswant G, Abhijit K, Pushpawati J, Vikas S et al. A systematic review of prescription pattern monitoring studies and their effectiveness in promoting rational use of medicines. Persp Clin Research. 2015;6(2):86-90. https://doi.org/10.4103/2229-3485.154005
23. Noto AR, Carlini EA, Mastroiani PC, Alves VC, Galduroz JCF, Kuroiwa W. Analysis of prescription and dispensation of psychotropic medications in two cities in the State of São Paulo, Brazil. Rev Bras Psiq. 2002;24(2):68-73. https://doi.org/10.1590/S1516-44462002000200006
24. Agência Nacional de Vigilância Sanitária – Anvisa. Formulário nacional da farmacopeia brasileira. 2a ed. Brasília, DF: Anvisa; 2012.
25. Lanchman L, Lieberman HÁ, Kanig JL. Teoria e prática na indústria farmacêutica. Lisboa: Fundação Calouste Gulbenkian; 2001.
26. Ansel HC, Popovich NG, Allen Junior LV. Farmacotécnica: formas farmacêuticas e sistemas de liberação de fármacos. 6a ed. São Paulo, SP: Premier; 2013.

27. Cavalcanti LC. Incompatibilidades farmacotécnicas na farmácia magistral: motivo, recomendação e uso terapêutico. 2a ed. São Paulo: Pharmabooks; 2008.

28. Kato FP, Souza MS, Gomes AJPS. Verificação do prazo de validade de cremes contendo hidroquinona preparados magistralmente: evidências do processo de oxidação. Rev Cienc Farm Basica Apl. 2010;31(2):199-203.

29. Mendonça CC, Silva ICL, Rodrigues KA, Campos MAL, Medeiros MCM, Silva ICL et al. Emulsões O/A contendo Cetoconazol 2,0%: avaliação da estabilidade acelerada e estudos de liberação in vitro. Rev Cienc Farm Basica Apl. 2009;30(1):35-46.

30. Pombal R, Barata P, Oliveira R. Estabilidade dos medicamentos manipulados. Rev Fac Cienc Saude. 2010;(7):330-41.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.