Challenges in research and development of phytomedicines in semisolid pharmaceutical forms

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The research and development of new drugs is a slow process that involves costs, requires physical, material and qualified human resources. The purpose of this study was to examine the research of recent years exposed on the challenges and obstacles to production and design of semisolid pharmaceutical forms from extracts or isolated compounds from medicinal plants. This study is an integrative review. The sample consisted of scientific articles found on the databases (Lilacs, Scielo, Science Direct and PubMed) from January 2002 to September 2012. The following descriptors were used: phytomedicines, stability of medicines and pharmaceutical preparations. The design of semisolid pharmaceutical forms, especially those in phytocosmetics, is relevant in Brazil, a major producer country by the pharmaceutical industry. However, due to the peculiarity of each drug and medicine, the study design may become one of the great difficulties of its accomplishment, as well as being a challenge to professionals in developing new pharmaceuticals. Thus, it can be suggested that despite the vast Brazilian biodiversity, there is no investment and cooperation in research and development of new medicines.

Key words: Phytomedicine, drug stability, pharmaceutical preparations.

INTRODUCTION

The use of products extracted from medicinal plants occurs since the dawn of civilization. From the late 19th century, natural products have been used on an industrial scale as a source of medicines. Despite advances, research on natural compounds for the pharmaceutical market is still restricted to academic institutions, government laboratories and/or small to medium businesses that produce herbal medicines. In this scenario, it highlights the production of semisolid pharmaceutical forms, mainly cosmetic, with Brazil being one of the major producing countries of that area (Seild, 2002). From the physicochemical point of view, pharmaceutical forms may be liquid, solid or semisolid consistency. In general, the semisolid pharmaceutical compositions are complex formulations and sometimes constitute substances whose structure also has some degree of complexity. Often, they are composed of two phases (water and oil), one continuous-external phase and the other dispersed-internal phase. In most cases, the active substances are dissolved in one of the phases, although occasionally the drug is not completely soluble in the system being dispersed in one or both phases, thus...
originating a three-phase system (Prista and Alves, 2003). The development of new formulations in the pharmaceutical and cosmetic market has been increasingly in recent years with emulsions being widely used for the incorporation of drugs and cosmetic actives, which emphasizes the use of semisolid pharmaceutical forms in the development of new therapeutic agents (Lange et al., 2009).

Research and development of new drugs is a long process that involves costs, requires physical structure, equipment and skilled manpower. Thus, due to the peculiarity of each drug and medicine, the study design can be one of the great difficulties in its implementation, and at the same time it is a challenge to professionals in the development of pharmaceutical products (Silva et al., 2009).

For Brazil being among the countries with the richest floras in the world, the search for medicinal plants and their inputs with applicability in dermal-formulations and other pharmaceutical forms is enabled (Pereira, 2008).

Therefore, this study aimed at analyzing the research of recent years that expose the challenges and obstacles to production and design of semisolid dosage forms from medicinal plants.

**Development of phytocosmetics in Brazil**

Currently, there is a trend of incorporating plant extracts in cosmetic formulations, in order to obtain formulas that can be used by a growing number of people looking for an effective alternative and less aggressive in the nature. This enhancement of plant caused increased demand for scientifically substantiated information about its safety and therapeutic efficacy (Cunha et al., 2009; Crespo, 2012).

On the world stage, numerous cosmetics industries seek innovation, making use of raw materials of diverse origins, mostly derived from plants, representing an alternative replacement of natural by synthetic materials. The incorporation of plant extracts on the bases for cosmetic purposes is a widespread practice, being of fundamental importance to the proper choice of the base to which the active ingredients of topical will be incorporated, thus ensuring the stability and absorption of the active ingredients and consequently, obtaining its pharmacodynamic effects expected (Sousa and Ferreira, 2010).

Other studies also mention the increasing use of natural products in the cosmetic industry, as the study by Fenner et al. (2006), which states that the plant extracts incorporated into cosmetic formulations, should be standardized, requiring rigorous study on the plant composition, or plants which comprise it, thus originating the phytocosmetics. According to Almeida and Bahia (2003), the plant extracts can be incorporated into various cosmetic preparations and depending on the chemical class of its active ingredients may be responsible for the product activity and may or may not change the cosmetic form and the rheological behavior of the preparation.

In Brazil, studies have been conducted on phytocosmetics in order to evaluate its stability and physicochemical properties. Thus, creams containing 5 to 10% glycolic extract of Isabel grape bagasse (*Vitis labrusca* L.) and gels containing 10% ground seeds were evaluated for 60 days, there being no physicochemical instability. An antiseptic formulation containing ethanol extract of *Plinia cauliflora* Mart. was also analyzed for stability showing satisfactory results in the physicochemical analysis (Oliveira et al., 2011; Sousa and Ferreira, 2010).

Phytocosmetics can be defined as a cosmetic containing natural active of plant origin, or an extract, fatty acid, essential oil, whose action defines the pharmaceutical activity of the product (Isaac et al., 2008).

The emulsions represent historically the oldest form of cosmetic application, being the first one cream that one created by Galeno for facial application (Isaac, 2009). Emulsion is a system consisting of two immiscible liquids, containing one aqueous or hydrophilic part and another oily or lipophilic, where one of the parts is dispersed in another as droplets, becoming homogeneous by the addition of surface-active substances which emulsify the system (Cefali, 2009).

A phytocosmetic must pass all stages of research as the proposition, the creation and development, including stability tests to ensure the activity throughout its lifetime. Stability is a parameter of validation needed to ensure the quality of phytocosmetic, although rarely described in standards validation of analytical methodology (Isaac et al., 2008).

Stability is defined as the time during which the medicinal product or the raw material considered individually maintain, within the specified limits and throughout the period of storage, and use the same conditions and features as when it was manufactured. The stability of pharmaceuticals depends on environmental factors such as temperature, humidity, light and other factors related to the product itself as physical and chemical properties of active substances and pharmaceutical excipients, pharmaceutical form and its composition, manufacturing process, type and properties of packaging materials (Brasil, 2005).

During the development of new cosmetic formulations, the stability testing should be performed. The study of stability helps to guide the development of the formulation and packaging material; provide input for improvement of formulations; estimate the validity and provide information for its confirmation; assist in monitoring the organoleptic, physicochemical and microbiological stability, producing information on the reliability and safety of products. Note that the stability tests involve preliminary stability testing, which aims at assisting and guiding the choice of accelerated stability testing formulation, which provides
data to predict product stability and shelflife (Brasil, 2004).

The National Agency for Sanitary Surveillance (ANVISA) also states it is necessary the quality control in the design of semisolid pharmaceutical forms, which is defined as the set of activities to verify and ensure that the necessary and relevant tests are performed and the material is not available for use and sale until it meets predetermined quality.

Quality control should not be limited to laboratory operations, but including all decisions related to product quality. It is the responsibility of manufacturers and importers to submit the cosmetic products to quality control (Brasil, 2007).

**MATERIALS AND METHODS**

The present study was designed as an integrative review, which is a method to gather and organize search results on a particular topic or issue, in a systematic and orderly manner, contributing to the deepening of the research theme (Roman and Friedlander, 1998). This study has established the following guiding question: “What are the challenges for design and production of semisolid pharmaceutical forms from medicinal plants?”

The sample consisted of scientific articles found in databases (Lilacs, SciELO, Science Direct and PubMed) from January 2002 to September 2012. The descriptors phytomedications, stability of drugs and pharmaceutical preparations were used in English and Portuguese.

The selection of articles was made by reading their abstracts and selecting those related to the research topic. As inclusion criteria, articles available in full and for free on selected databases in English, Portuguese and Spanish were used. Dissertations, theses, abstracts in conference proceedings and/or books, as well as the repeated articles were excluded from the sample. For analysis of the articles was reading the abstracts and selecting those who reported the design of phytomedicines in semisolids forms, emphasizing the stages of development of phytomedicines.

**RESULTS AND DISCUSSION**

The study sample composed of 15 articles, most from Lilacs database, as shown in Table 1. On the database (Science Direct), after searching with keywords phytomedications, drug stability and pharmaceutical preparations, 31 articles were found, but these articles were not related to the theme proposed in this study. On the LILACS database, among 1318 articles found, only 12 were related to the theme. On another database searched, SciELO, only one article related to the topic was found but excluded for having been found in other databases. Finally, the research on Pubmed, showed 41146 articles with three items being related to the research problem.

Most publications was conducted between 2009 and 2010 in Portuguese and reported, among other aspects, methods and techniques to control production and phytomedicines. The articles demonstrate the importance of conducting preliminary studies on stability and quality control of phytomedicines as a key step in the production and design of these pharmaceutical forms.

It is known that the major sources of biodiversity are rainforests located in developing countries like Brazil, which holds about a third of the world flora. However, developed countries like the United States (U.S.) and Japan are the ones that most manufacture and market...
natural products, given their greater investment in research and development of pharmaceuticals. In this context, it is expected that new products can be produced in Brazil from native species through institutional commitments (universities and companies), with the application of resources to ensure that the work of experts in the fields of botany, biology, pharmacy, medicine, chemistry, among others (Klein et al., 2009).

The design of semisolid pharmaceutical forms, especially phytocosmetic, gains prominence in Brazil, one of the major producing countries in the field of cosmetics. This large-scale production can be related to the strong ties with companies that are sources of natural products for preparation of formulations, as well as due to the commitment that producing industries have with the conservation of natural resources and promotion of sustainable development practices, which demonstrates that good relationships between companies and ensuring of raw material are important for success in the production of phytomedicines (Seild, 2002).

The production of phytomedicines necessarily passes through the stage of research and development (R & D) of drugs. Studies point to the idea that the success of R & D activity depends largely on its planning and organization. This requires the definition of objectives, adequate budget, leadership, effectiveness, safety, size of the research team and ease of internal and external communication. Moreover, the entire process involved in the production should be monitored, including the environment control, manufacturing control and final control of production. The failure of these criteria, due to poor human resources and/or materials can be an obstacle in the design of pharmaceutical forms (Cardoso et al., 2002; Martinelli et al., 2005).

According to the protocols of drug stability, the parameters evaluated in the products subjected to stability tests should be defined by the formulator and depend on the characteristics of the test and components used in the formulation. The organoleptic characteristics determine the parameters of acceptance of the product by the consumer. In general, the appearance, color, flavor, smell and feel to the touch were evaluated. The product must remain intact in the test while maintaining its original aspect in all conditions except at high temperatures, freezer or cycles in which small changes are acceptable. The color and smell should remain stable for at least 15 days to sun light. Minor changes are acceptable at elevated temperatures.

The rheological features are important properties to consider in the manufacture, storage and application of topical products. Studies on rheology of pharmaceutical formulations for topical use have become increasingly frequent in research conducted by the scientific community, because even today it is clear that the physical stability of a formulation is fundamental to the quality control, consumer acceptance and its effectiveness (Correa et al., 2005).

Previous studies have already demonstrated the importance of the rheology of the pharmaceutical product, stating that the determination of the rheological behavior of the formulation aids in the evaluation of the physicochemical nature of the vehicle in such a way that makes it possible to detect early signs of physical instability allowing control quality of constituents, testing formulations and final products (Cefali, 2009).

Cosmetic products may also be subjected to thermal analysis comprising a group of techniques by which a physical property of a substance or its reaction products is measured depending on temperature, while the substance is subjected to controlled propagation of the temperature. This analysis enables a wide range of application for physical measurements, study of chemical reactions, thermal stability evaluation, determination of the chemical composition of materials and development of analytical methodology (Guillen et al., 2006).

Thermoanalitytical techniques have great importance in cosmetic scope due to the large variety of applications and the most used methods are the differential scanning calorimetry (DSC), thermogravimetry (TG) and derivative thermogravimetry (DTG). Thermal analysis can be used both in control of raw material as the finished product having potential use in the development and characterization of new products (Guillen et al., 2006; Silva et al., 2007).

The different phytocosmetic formulations still require testing related to their stability, as shown by different studies. The formulation of a proniosomal gel, with the aim of improving its transdermal permeation, brought positive results with improved permeation. In this study, there was a need for short-term stability tests, which demonstrated the chemical and physical stability of the product. Studies on the development of a gel from the extract Cacalia hastata L. also show the results of phytomedicines’ stability indicating that the product is stable at room temperature with preserved appearance and viscosity (Thomas and Viswanad, 2012; Jambaninj et al., 2012).

In a study with a cream developed from Allamanda catharica L. was also performed in accelerated stability tests, lasting 60 days. The samples were subjected to heating in an oven, cooling in refrigerators, exposure to light radiation and environment, with temperature control being subsequently analyzed, showing a positive result to the product stability (Crespo, 2012; Terra et al., 2009).

Faced with these new requirements with respect to the development and validation of stability indicating method, pharmaceutical industries and the Research & Development Centers must perform stress tests in order to isolate, identify and characterize the degradation products obtained by variable adverse conditions.

However, due to the peculiarity of each drug and medicine, the study design may become one of the major difficulties of its accomplishment at the same time it is a challenge necessary to professionals in the development of pharmaceutical products (Silva et al., 2009).
Also, regarding the stability studies, the need for better packaging and storage conditions of raw materials and finished products in masterful establishments, lighting conditions and packaging standardization are scored as difficulties to perform more effective stability testing (Kato et al., 2010).

Conclusion

The development of phytomedicines, especially those phytocosmetic, is increasing in Brazil, but there are still many barriers to production and design of these semisolid dosage forms. The study showed that lacked investment and cooperation in research and development of new drugs, despite the vast Brazilian biodiversity. The integration between business and universities and research centers is still a difficulty for production and design of pharmaceutical forms. There is also shortage of human and material resources in the studies of drugs stability, necessary procedure for their design.

Conflict of interest

Authors declare that they have no conflicts of interest.

REFERENCES


