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RESEARCH ARTICLE

STANDARDIZATION OF THE EXCIPIENTS IN GELATIN CAPSULES HARD OF DRY EXTRACT OF PASSION FRUIT (*PASSIFLORA INCARNATA*) PRODUCED IN THE LIVING PHARMACY PROJECT IN SOBRAL-CE

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ABSTRACT

The Living Pharmacy Project is the first pharmaceutical social assistance project developed in Brazil based on the scientific use of medicinal plants. Among the standardized formulations in gelatin capsules hard, stands out the dry extract of passion fruit. The formulation of these capsules requires an addition of excipients, that has important role in the quality, safety, and performance of the drug. The purpose of this study was to standardize the excipients for capsule formulations produced in the Living Pharmacy Project. Was conducted a literature review of the various excipients and herbal medicines and analysis of the package leaflet of the drugs. Thirty capsules of the phytotherapeutic agent were produced and subjected to quality control to evaluate the average weight variation, including the coefficient of variation and standard deviation. The suggested excipients for the passion fruit formulation were sodium starch glycolate (8%) as a disintegrant, magnesium stearate (0.5%) as a lubricant, sodium lauryl sulphate (2%) as wetting agent, colloidal silicon dioxide (0.5%) as a glidant, pharmaceutical talc (1%) as an adsorbent, pharmaceutical starch (22%) as a hydrophobic diluent, and lactose monohydrate (66%) as a hydrophilic diluent. All quality control results met the pharmacopoeia specifications.

INTRODUCTION

In a pioneering initiative, Professor Francisco José de Abreu Matos, pharmaceutical, phytochemical and researcher at the Federal University of Ceará (CUF), implemented the Living Pharmacy Project aimed to serve small communities, spreading the popular use of medicinal plants and extemporaneous preparations in the region (Michiles, 2004). It is the first pharmaceutical welfare project based on the scientific use of medicinal plants developed in Brazil, aiming to produce herbal medicines accessible to the poor (Matos, 1998). Since its creation in the state of Ceará, it has become a reference for the Brazilian Northeast and later for the whole country (Diniz *et al*., 1999).

The use of nature for therapeutic purposes is as old as human civilization. Historically, medicinal plants are considered important in discovery of new drugs, being in the plant kingdom the greatest contribution of medicines. Phytotherapy comprises thus a link of complementary therapies, which are techniques to the health care of the individual, whether in prevention, treatment or cure, considering the man as a whole and not a set of isolated parts (Bastos and Lopes, 2010; Brasil, 2012b).

Among the formulations standardized by Living Pharmacy design can be highlighted handling semi-solid dosage forms such as ointment mastic peppermint and rosemary soap; oral liquid formulations such as syrup Cumaru, Chamba syrup and elixir of mastic; and solid oral forms, such as hard gelatin capsules (Matos, 1998).

Among the hard gelatin capsules may be noted within the project, the capsules containing Dry Extract of Passion Fruit (DEPF) (Passiflora incarnata). This phytotherapic it's used in various pharmaceutical products, including compounding formulations produced in pharmacies. Although plants traditionally used in herbal medicine, its use requires criteria,

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since they have contraindications and can lead to severe adverse reactions (Bara *et al*., 2006).

The drugs, rarely, are administered singly, usually are part of a formulation combined with one or more non-pharmacological agents, which are referred to as pharmaceutical excipients. Excipients can thus perform various functions in a pharmaceutical formulation. According to its role in formulations, these can be classified as binders, diluents, disintegrants, lubricants, binders, surfactants, coating materials, coloring agents, buffers (eg .: alkali phosphates), among others (Ansel *et al*., 2007; Gad,2008).

For handling gelatin capsules it is necessary an amount of drug prescribed by a qualified professional, and an additional amount of excipients. The magistral pharmacist need to have technical knowledge to the calculations of the amounts of drugs and excipients to be placed in the capsules. There are several methods for the calculation of these quantities, among them we can mention the volumetric method, also known as a method of the test tube, to be the most accurate method among all (Ferreira, 2008).

The approximate capacity for a given capsule size depends largely on the density of each powder, and this capability is provided in milliliters (ml) (Trompson and Davidow, 2013). The elements are available in eight sizes, with different capacities, being designated by numbers (Table 01).

Table 01 Capsule size and its approximate capacity in mL (Marques, 2008)

Capsule size	Capacity (mL)
000	1,37
00	0,95
0	0,68
1	0,5
2	0,37
3	0,3
4	0,21
5	0,13

Excipients have an important role in the quality, safety and performance of drugs and influence in vitro and in vivo release of drugs from the capsules (Villanova and Sá, 2009).

Ensuring the safe and effective use of herbal medicine involves a set of physicochemical and microbiological analysis of raw materials and the finished product, as a preliminary step to achieve a quality standard required for a drug (Bata *et al*., 2006). For quality control of solid oral dosage forms should be performed at least the tests recommended by the Brazilian Pharmacopoeia 5th edition or, failing that, another official compendium as is treated in the RDC nº 37, 2009, which deals with the admissibility of the pharmacopoeia foreign, recognized by ANVISA (Brasil, 2008).

The Biopharmaceutical Classification System (BCS) is based on the fundamental properties that govern drug absorption, particularly on the basis of the permeability and solubility parameters. When combined with the dissolution of the drug, BCS takes into consideration three important factors that affect the rate and extent of absorption of solid dosage forms for immediate release: dissolution, solubility, and permeability. The main purpose of BCS is to estimate the pharmacokinetic in vivo performance of a drug from the permeability and solubility data in order, thereby, help in decision-making in cases of exemption from bioequivalence studies (Amidon *et al*., 1995, Karalis *et al*., 2008).

It has been proposed by Ferreira (2008), an algorithm for selection of excipients for gelatin capsules (Attachment 01), is a practical and complementary flowchart to the Biopharmaceutical Classification System, to decide judiciously the form and technique they will be added to the composition of the formulation, based on the concentration of the active substance.

Thus, this study aimed to suggest, through a literature review of the excipients used in the formulation, standardization of excipients for a herbal formulation containing DEPF in gelatinous hard capsules, according to the Biopharmaceutical Classification System (BCS). After handling the capsules were made some quality control tests, such as average weight variation limit, coefficient of variation, standard deviation and variation of the theoretical contents of the capsules.

MATERIALS AND METHODS

Standardization of excipientes

Excipients were standardized based on the findings in the literature and assets to passion fruit capsules, standardized and manipulated the Living Pharmacy Project, located in the city of Sobral-CE. Research materials used in the literature were articles contained in Scielo databases, CAPES journals and dissertations, doctoral theses and package inserts of drugs available.

Calculation of the amount of active and excipient

To determine the amount of active and excipient is necessary to know the bulky density and packing density, to perform the arithmetic mean of both. a measuring cylinder of 100 ml, which was measured 50 mL powder, for later weighing this apparent volume obtained was used. From the known weight and volume was calculated densities of the powders without compression (Bulky Density) (Brasil, 2012a). Shortly thereafter, the sample was subjected to successive compressions to determine packing density, calculated by the same equation of Equation 01 (Brasil, 2012a).

Equation 01. The equation determines density through mass and volume, where D = density (g / ml); m = mass (g); V = volume (ml).

$$D = m/v$$

Determination of Bulky Density (BD)

To determine the bulky density, the active substance powder was added in 50 ml volume in a 100 ml beaker without compression, and held weighing in an analytical balance. The

obtained mass was noted, for conducting further calculating the density (Equation 01), it was performed in triplicate, which then was done the arithmetic mean of three densities (Japanese Pharmacopoeia, 2006).

Determination of Packing Density

To determine the packing density of the powder substance was added in 50 ml volume in a 100 ml beaker and held weighing in an analytical balance. The obtained mass was noted, were soon made hundred (100) compacts at a height of 10 (ten) centimeters in height on a flat surface of wood, for carrying out subsequent calculation of density (Equation 01), this was accomplished in triplicate, which then was done the arithmetic average of the three densities obtained (Japanese Pharmacopoeia, 2006).

Conversion of Real Density in Volume

After performing the arithmetic mean of triplicate bulky density and the average of triplicate packing density was calculated using the arithmetic average of these densities, obtaining a value of the actual density of the substance. This calculation was performed to determine the mass in grams of assets (Passion Fruit 250 mg) and standard excipients, to then find the volume that will be occupied in the capsule (Silva, 2013).

Capsules Manipulation

The capsules are handled by the volumetric method, encapsulating manual calculation after active excipient and then was performed weighing and mixing of the constituents (drug and the excipients) in a suitable powder mixer automatic (POWDERMIX®) (Rosa *et al*., 2010).

From the calculations made for the volume of the capsule, was selected manual Capsule #1 for passion fruit 250 mg. They were prepared 30 passion fruit capsules, with concentration of 250 mg.

The powder mixture containing more excipients drug, after being homogeneously mixed was placed on the encapsulating chosen. With the aid of a plastic spatula, the powder was introduced into the body of uniformly capsules. After filling the body of the capsule, the lid was put and then each capsule individually closed by manual pressure.

The capsules were removed from the encasing and then a paper towel were cleaned externally for removal of residual dust. Soon after, the capsules were subjected to quality control.

Quality Control Testing

Determination of Average Weight

Was weighed individually ten units capsules containing DEPF handled intact and determined the average weight in grams, and inserted into the following equation (Equation 02).

Equation 02: Equation to determine the average weight for these capsules manipulated Where: Wcáps. 1, Wcáps.2, Wcáps.3 (...) Wcáps.10 = manipulated weights of each capsule unit (Brasil, 2012).

$$Waverage = \frac{Wcaps.1 + Wcaps.2 + Wcaps.3 + \cdots + Wcaps.10}{10}$$

The value obtained was compared with the value for the assessment criteria for determining the weight for solid dosage forms in single doses (Table 02) (Brasil, 2012a).

Table 02 Evaluation criteria determining the weight for solid dosage forms in unit doses (Brasil, 2012a)

Hard Capsules	
Average Weight	Variation Limit
Less than 300 mg	± 10,0%
300 mg or more	± 7,5%

Determination of Standard Deviation

It was calculated by applying the following equation (Equation 03) (Filho, 1999).

Equation 03: Standard Deviation Equation for the calculation of individual gelatinous hard capsules. Where: Pcáps. 1 = weight of each drive manipulated capsules; n = number of hard capsules manipulated employed in the determination of average weight (Brasil, 2012a).

$$DP = \sqrt[2]{\left(\sum_{i=1}^{n}\left(\frac{Wcáps.i - Waverage)^2}{n-1}\right.\right.}$$

Coefficient of Variation or Relative Standard Deviation

It was calculated from the ratio between the standard deviation (Equation 03) and mean weight (Equation 02) multiplied by 100 (Equation 04) (Brasil, 2010; Brasil, 2012a).

Equation 04: Variation Coefficient Equation. Where: SD = standard deviation; Waverage = average weight of the capsules obtained (Brasil, 2012a).

$$VCE = \frac{SD}{Waverage} x100$$

Variation of Theoretical Contents of Capsules

To determine the variation of the theoretical contents of the capsules it was weighed individually 20 empty capsules, and then calculated the arithmetic average as shown in Equation 05 (Brasil, 2012a).

Equation 05: Average weight Equation of Empty Capsules (Brasil, 2012a).

$$Waverage.caps.empty = \frac{(Wcaps.empty1 + Wc.empty2 + \cdots + Wc.empty20)}{20}$$

It was also calculated the theoretical weight of the capsules, which is obtained by summing the average weight of empty capsules weight of the excipient and the drug weight (Equation 06) (Brasil, 2012a).

Equation 06: Equation to calculate the Theoretical Average Weight of capsules (Brasil, 2012a).

$$Wtheoretical = Waverage - caps.empty + Pexcipients + Pdrug$$

From the variation of the content of capsules was estimated the maximum and minimum theoretical quantity of powder, according to the extremes of weights obtained in the weight of the capsules. Thus, they took up the capsule lighter weights and the heaviest according to Equation 07 (Brasil, 2012a).

Equation 07: Equations of Theoretical Minimum and Maximum Amount Theoretical Where: Wcapsules lighter = is the smallest individual weight observed in weighing the capsules manipulated to determine average weight; Pcapsule heavier = is the single largest observed weight at the weigh capsules manipulated for determination of average weight (Brasil, 2012a).

$$Amount.\min = \frac{Wcaps.lighter}{Wtheoretical} x\ 100$$

$$Amount.\max = \frac{Wcaps.higher}{Wtheoretical} x\ 100$$

RESULTS AND DISCUSSION

Excipients Standardization Tip for capsules containing DEPF

From the theoretical survey of leaflets medicines and supplies (Sousa *et al*., 2008; Nascimento *et al*., 2009; Zeraik *et al*., 2010) a proposal for standardization of excipients suggested for Passion Fruit 250 mg. The choice of excipients was based on the physicochemical characteristics of the dry extract of the herbal medicine.

The DEPF was considered a hygroscopic powder of low solubility and low permeability. According to the inserts of processed medicines, it can be assumed that the powder has difficulty in solubilizing the stomach, intestinal absorption and due to its phytochemical marker expressed in flavonoids (vitexin).

Table 03 excipients standardization Tip for capsules containing 250 mg ESM produced in Pharmacy School Project

Components	Function	Percentage
Sodium lauryl sulfate	Wetting Agent	2,00 %
Sodium Starch Glycolate	Disintegrant	8,00 %
Talc Pharmaceutical	Adsorbent	1,00 %
Colloidal Silicon Dioxide	Sliding	0,5 %
Magnesium Stearate	Lubrificant	0,5 %
Lactose	Diluent	66,00 %
Pharmaceutical Starch	Diluent	22,00 %

Table 03 below shows the formulation of standardization proposal for handling hard gelatin capsules containing 250mg Passionflower.

This proposal has taken into consideration in addition to the physicochemical properties, the biopharmaceutical classification of passion fruit, being classified as a powder belonging to Class IV, selecting excipients that can positively influence the solubility and permeability and consequently the bioavailability of active (Almeida *et al*., 2013).

The choice of excipients was made from data obtained in the literature, and selected the most suitable excipients for the biopharmaceutical needs of the asset (Rosa *et al*., 2010). excipients classes used to standardize suggestion include: Wetting agent, disintegrator, Absorbent, sliding, lubricant and Thinner.

To improve the solubility and drug absorption in the stomach, it has been chosen as wetting agent, sodium lauryl sulfate (SLS) at a concentration of 2%. The concentration was chosen based on the algorithm proposed by Ferreira (2008), which for active class IV, the concentration between 100 to 1000 mg, a wetting agent is used at a concentration of 2% (Appendix 01). Being a tense anionic active, the LSS acts reducing the surface tension and thus improving the wettability, favoring the penetration of water into the solid mass, facilitating dissolution of the drug (Zeraik *et al*., 2010).

To improve the solubility of the formulation used a disintegrating agent, sodium starch glycolate at a concentration of 8%. The concentration was chosen based on the same algorithm (Appendix 01), which for active class IV, the concentration between 100 to 1000 mg, a disintegrating agent is used at a concentration of 8%. This excipient is intended to improve the compressibility, disintegration and the flow of powder to increase the surface area exposed to gastrointestinal fluids by water uptake followed by rapid and large swelling (Aulton, 2005; Pessanha *et al*., 2012). Increasing drug solubility facilitates the disintegration thereof with an excipient facilitator of the dissolution (Miranda *et al*., 2013). Thus, in systems controlled by swell, the active principle dispersed or dissolved in the polymer matrix is able to diffuse into, and released slowly when the polymer system comes into contact with a solvent or compatible fluid so that occurs swelling of the polymer (Devi*et al*., 2011).

Because it is a formulation of herbal medicine, one of the active properties is to be a hygroscopic powder, requiring the use of the pharmaceutical powder as absorbent at a concentration of 1.00%. The concentration was chosen based on the algorithm (Appendix 01). Even been described in the literature that its main function is lubricant, talc also has drying effect, favoring the stability of the formula (Miranda *et al*., 2013). Due to the hydrophobic nature can also retard the dissolution of the drug, increasing the permeability (Ferreira, 2008).

To improve the flow of powder mixture was added colloidal silicon dioxide at 0.5%. The concentration was chosen based

on the algorithm (Appendix 01). For this agent has sliding functions, desiccant and nonstick, improving the mixing of powders, facilitating their flow to the capsule (Guimarães and Moraes, 2013). This excipient very small particles, when dispersed in water aggregates form constituting a three-dimensional lattice (Aulton, 2005).

As lubricant, the magnesium stearate was chosen for improving the post flow properties of the formulation, reducing the friction of the powder with the mixture of equipment parts during handling. This lubrificant was used at a concentration of 0.5%. The literature recommends its use in concentrations of 0.25% to 2% and can not exceed 2%, because of its lipophilic characteristics that may impair the solubility of the drug, because it delays the penetration of liquid components in the formulation, so that once dissolved the capsule shell in gastrointestinal fluids, yet remain a post aggregate (Aulton, 2005; Ramos and Morais, 2013).

Diluents are pharmacologically inert substances used for the desired volume filling of capsules and tablets (Gonçalves, 2009). The formulation of thinners were the lactose monohydrate and the pharmaceutical starch. Diluents are excipients which are present in the formulations at higher concentrations (Villanova and Sá, 2009). The lactose monohydrate, having a hydrophilic chemical nature has been used to increase the solubility of the active. The pharmaceutical starch, having a hydrophobic nature, was used to increase the absorption in the intestinal medium. And a diluent of vegetable origin, so it is used in manipulating containing dry extracts (Miranda *et al*., 2013). the use of two solvents, a hydrophilic and a hydrophobic, for thus will not influence markedly in solubility and permeability of the asset is required (Ferreira, 2008).

The present standardization suggestion also took into account the standardization of the excipients present in the package inserts of the manufactured drugs, serving as basis for the proposed standardization. The pharmaceutical forms containing Maracujá as are sold on the national market an oral suspension dosage form, capsules and tablets, with the target pharmaceutical form of this study is the pharmaceutical hard gelatin capsule form, leaflet containing the findings Passion fruit are listed (Table 04 and Table 05) below with a brief analysis of the formulations.

Table 04 Drug A, excipients and their possible functions

Component	Function	Quantity
Colloidal Silicon Dioxide	Sliding	U
Magnesium Stearate	Lubrificant	U
Microcrystalline Cellulose	Diluent Hydrophobic	U

U = Uninformed

Regarding the formulation of the medication, it can be assumed some technical information about its biopharmaceutical classification. In this formulation was used a lubricant to improve permeability, a hydrophobic diluent to improve permeability and a glidant to improve powder flow property (Ramos and Morais, 2013).

Table 05 - Drug B, excipients and their possible functions

Component	Function	Quantity
Colloidal Silicon Dioxide	Sliding	U
Magnesium Stearate	Lubrificant	U
Talc Pharmaceutical	Absorbent	U
Microcrystalline Cellulose	Diluent Hydrophobic	U
Croscarmellose Sodium	Disintegrant	U
Polyvinyl Alcohol	Solubilizing	U
Iron Oxide Yellow	Coloring	U
Titanium Dioxide	Opacifier	U

U = Uninformed

Regarding the formulation of B drug, it can be assumed more information about techniques for their biopharmaceutical classification. In this formulation there is a solubilizer and a disintegrant, which will improve the solubility of phytochemical marker. It has a glidant, a lubricant and an absorbent to improve the permeability of the phytochemical marker. It was used, a hydrophobic diluent and a lubricant to improve the permeability of the drug. Dried extracts are known hygroscopic powders (Ferreira, 2008), justifies the use of the pharmaceutical powder formulation to be also hydrophobic in nature. The slider is used to improve powder flow. In the case of a tablet formulation, there was the use of a colorant to impart color to the tablet (Guimarães and Moraes, 2013) and an opacifier to give a white aesthetic appearance (Saleiro *et al*., 2010).

Manufacturing and Quality Control of Hard Capsules containing Dry Extract Passion fruit (DEPF)

They were manipulated 30 capsules in Solids Laboratory of the Pharmacy School of INTA Colleges. After weighing the amount of excipient and the amount of the active, both in grams, they were placed into a suitable plastic container to promote mixing of powders, shortly thereafter, the mixture was placed in automatic powder homogenizer. After five minutes of mixing, the powder was removed from the homogenizer placed on the previously selected Manual Capsule.

Of the thirty (Saleiro *et al*., 2010) units compounded capsules, it was removed a 10-sample (ten) units for performing quality control (Brasil, 2012a).

Of the 10 units submitted to quality control was calculated the average weight variation limit, standard deviation, coefficient of variation and variation of the theoretical contents of the capsules. All values are expressed in the following table (Table 06) (Brasil, 2012a).

The determination of the average weight was made according to criteria of the National Formulary, using 10 capsules for determining (Brasil, 2012a). From the obtained values of individual capsules, it was observed that the average weight of the capsule was 0.4086 g. The average weight provides an indicator for the quality of the encapsulation process the drug and the rate of handling efficiency, through the complete body of the capsule filling indicating a result of the appropriate mean weight. The limit of higher variation and allowed lower, considering a deviation of ± 7.5% of the average weight.

Table 06 Trials quality for hard gelatin capsules containing DEPF at a concentration of 250 mg

Sample	Weight of the filled capsule	Individual variation coefficient	Error ± 7.5%	Error ± 10.0%
P01	0,413	1,08	ACCORDING	ACCORDING
P02	0,414	1,32	ACCORDING	ACCORDING
P03	0,415	1,57	ACCORDING	ACCORDING
P04	0,412	0,83	ACCORDING	ACCORDING
P05	0,4	2,10	ACCORDING	ACCORDING
P06	0,401	1,86	ACCORDING	ACCORDING
P07	0,405	0,88	ACCORDING	ACCORDING
P08	0,412	0,83	ACCORDING	ACCORDING
P09	0,406	0,64	ACCORDING	ACCORDING
P10	0,408	0,15	ACCORDING	ACCORDING
Total sum	4,086	**Error - 7.5%**	0,378	HIGHEST VALUE
Average weight	0,4086	**Error + 7.5%**	0,439	0,415
Standard deviation	0,005420127	**Error - 10.0%**	0,347	LOWER VALUE
Coefficient of variation	0,0132651177	**Error + 10.0%**	0,470	0,4
Average Theoretical (g)	0,4086	**Variation (+/-)**	0	0,00%
Theoretical content		101,57%	97,90%	100,00%

For the above table (Table 06), it was found that all capsules were within the acceptable range limit, wherein the maximum value was 0.415 g, and the minimum value was 0.400 g.

From the average weight of the capsules, it was calculated standard deviation and the variation coefficient of the sample, which was 0.00542 and 0.01326 (1.32%), respectively. Only the average weight of the capsules does not imply an outcome of good quality for quality control testing. The purpose of calculating the standard deviation is to find a number that indicates a dispersion of individual values around the mean of a set of measures. It is known that the lower the standard deviation value indicates a good uniformity of capsule contents (Rosa *et al*., 2010).

The coefficient of variation, also called relative standard deviation is used to express the percentage ratio of standard deviation to estimate the average of the individual values obtained. From Table 06 it can be seen that the coefficient of variation of capsules 250 mg of ESM was considered satisfactory, because it is within the reference value recommended by the National Formulary and should not exceed 4%.

The values of maximum and minimum theoretical content obtained were 101.57% and 97.90%, respectively (Brasil, 2012a). According to the National Formulary (Brasil, 2012a), the maximum and minimum theoretical amounts calculated contents of the capsules will be contained in the range of 90 to 110%. Based on this, the manipulated capsules were considered consistent with the results (Brasil, 2012a).

CONCLUSION

The study suggest a pattern of a herbal medicine for the Living Pharmacy Project, allowing the scientific and proper use of excipients for handling capsules, taking into account the physicochemical properties of the phytochemical marker. The standardization is necessary to improve meet the solubility and permeability of the active ingredient in a formulation as excipients will influence the bioavailability of the drug, thus in the same therapeutic response.

It is very important the realization of quality control in routine preparation of capsules, since it allows prove to standardize the contents of the capsules, ensuring product effectiveness, quality and safety.

Given all that has been addressed, as a primary study, the major difficulty was the lack of technical information found in the literature regarding the standardization of herbal excipients, the main technical information found in unofficial sources.

The study showed a high scientific relevance and highlights both the characterization of the algorithm, as the methodological segment through the use of herbal medicines. Demonstrating that the system Biopharmaceutical Classification can be a tool for useful herbal manipulation.

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