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Research Article

Pharmacotechnical Development of Polymer Coating for *Valeriana Officinalis L.* Tablets by Quality by Design

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Abstract

Solid dosage forms are the first choice of oral drugs because they allow a single and precise dose of the drug. The pharmaceutical industry as a whole is always developing ways to improve over traditional ways, with the aim of promoting the benefit, safety, acceptance, and adhesion of patients during therapy. Tablet coating refers to the application of a material over the outer surface of tablets, with the intention of providing greater stability and quality compared to uncoated tablets. Therefore, the main research proposal was to develop the coating for *Valeriana officinalis L.* tablets, to mask the unpleasant taste and odor of their cores, also acting to protect against moisture, which will disguise the differences in the appearance of the marketing tablets from a Quality-by-Design perspective. Polymeric coatings with different colors have been proposed to differentiate tablets at 50 and 100mg doses. Pharmacopoeial tests were conducted to define the most appropriate coating for the industry's marketing sector. It was possible to obtain coated tablets with greater stability in relation to the cores, since the developed coating provided integral and uniform coverage, providing adequate differentiation of the 50 and 100mg tablets.

Keywords: Solid oral drugs; Polymer films; Pharmaceutical quality system; Hypnotics; Anxiolytic

Abbreviations: CC: Change Control; CMA: Critical Material Attributes; CPP: Critical Process Parameters; CQA: Critical Quality Attributes; FMECA: Failure Modes, Effects and Criticality Analysis; GMP: Good Manufacturing Practices; PCH: Product Change History; PEG: Polyethylene Glycol; PVA: Polyvinyl Alcohol; QbD: Quality-by-Design

Introduction

Drug delivery science and technology are continually being investigated by the pharmaceutical industry to obtain medicines with superior biopharmaceutical properties that promote efficacy, safety, and patient adherence during pharmacotherapy [1-3]. The pharmacotechnical development of new technologies for drug delivery requires intense research efforts, vast knowledge of Pharmaceutical Sciences, and market skills, with an emphasis on pharmacoeconomics. In addition to improving biopharmaceutical attributes, a new technology needs to offer advantages in terms of cost-effectiveness, so that the product is effective, safe, and competitive in the pharmaceutical market in order to become a first-choice alternative for the prescriber for the target disease. Tablets are one of the most common pharmaceutical forms in clinical practice because of their dosage convenience, stability, efficacy, biopharmaceutical safety, and attractive cost as a drug release system, which is why several studies have corroborated advances in these systems [1,4-9].

Tablets are obtained by compressing uniform particles after careful study of the compatibility between pharmaceutical ingredients. From this perspective, the Quality by Design (QbD) approach has been successfully applied to optimize processes and time and reduce costs [10]. For example, it is essential to know the Critical Material Attributes (CMA) to outline the Critical Process Parameters (CPP). The powder behavior in the compression process defines the parameters inherent to the process technology, such as the strength of the punches or compression route (direct/indirect, dry/wet), as well as the ingredients and use

concentrations [1,11]. Pharmaceutical solids do not always present fully satisfactory characteristics for compression; for example, those that present elastic deformation return to their original state after the applied force ceases, making the integrity of the pharmacotechnical unit unfeasible [2,12].

One effective strategy for obtaining tablets with adequate mechanical resistance is coating. This technology involves the application of a biocompatible material on the external surface of tablets, with the proposal of greater stability and quality when compared to uncoated tablets [1,11]. Tablet coating is also used as a controlled drug release system [13-17] and allows different coloring between pharmaceutical specialties from the same manufacturer, a successful strategy in risk management in Good Manufacturing Practices (GMP) for drug products [18]. The different coloring between pharmaceutical products, for example, the same drug and pharmaceutical form, at different doses, helps in the punctual identification of the batch on the production line, mitigating the risk of changes during packaging. In this context, *Valeriana officinalis* var. latifolia. tablets are mentioned. It is an herbal medicine. Some species of Valerian are widely used as mild sedatives and adjuvants in hypnotic treatment in established clinical practice in European and American countries [19]. The leaves and stems of *Valeriana officinalis L*. have at least fifty-nine compounds, including 19 iridoids, isolated and characterized by Liu et al. [20], confirming the pharmacological potential of this plant, especially in sleep disorders.

Among the reasons for coating *Valeriana officinalis L*. tablets, the highlights mask the unpleasant taste and odor of the nucleus, protect against humidity (especially as it is an herbal medicine), mask irregularities or heterogeneity in the appearance of the nuclei, and interfere with patient adherence to treatment. It should also be noted that the application of coating reduces the chance of cross-contamination during production, as it reduces the detachment of the powder from the tablets [1,9,11,21]. The coating proposal is a challenge for the pharmacotechnical development. The use of QbD tools is very useful for pharmaceutical production, in particular for testing coating formulations, as some parameters are critical in the process. Therefore, the application of polymeric coating on *Valeriana officinalis L*. tablets with monitoring of variables by QbD is an innovation for manufacturing. Coating technology is a viable strategy to obtain tablets with superior stability and biopharmaceutical properties. This is a common practice in the pharmaceutical industry and requires continuous improvement in the formulation and unit operations involved. Thus, this research was developed in view of the need to improve the coating for *Valeriana officinalis L*. tablets, using colored film with the aim of differentiating the formulations at doses of 50mg and 100mg, as a risk management strategy, in GMP, and patient safety (clinical practice).

Material and Methods

To design the formulation coating, the QbD principles were adopted [10]; thus, four different coating colors were proposed for *Valeriana officinalis L*.: 50mg tablets, green, blue, yellow, and white.

Materials

The ingredients used were dry extract of *Valeriana officinalis L*., colloidal silicon dioxide, magnesium stearate (0.25mm mesh), microcrystalline cellulose 102, lactose super tab 22AN, croscarmellose sodium (1.0mm mesh), Opadry® ll (polyvinyl alcohol - PVA + polyethylene glycol - PEG + talc), brilliant blue dye, yellow iron oxide dye, titanium dioxide, 30% simethicone and water.

Core obtained

Tablet cores were obtained at the pilot scale. The powders were weighed and normalized to ensure homogeneity of the particle size. The powders were subjected to the mixing process in a "V" mixer (Lemaq®), 15rpm, for 10 minutes and then for another 5 minutes after adding magnesium stearate. After mixing, the powders were subjected to compression with the aid of a rotary compressor machine (Lawes Manu® 2000/14ps), oblong shaped punch 14mmx7.5mm smooth.

Core quality control

The cores of *Valeriana officinalis* tablets (50mg) were subjected to physical quality tests in accordance with the general methods described in the Brazilian Pharmacopoeia [22]. The weight, hardness (Erweka hardness meter, 1EQSO-208), and friability (Nova Ética friability meter) were determined.

Obtaining the film coating

The coatings were composed of polymers, plasticizers, dyes, and solvents. The film was obtained by incorporating the raw materials into the solvent through mechanical stirring for 45min.

Tablet coating

The coating deposition technique was performed using the spray method, where a thin layer of the coating suspension was deposited on the surface of the tablet core by a rotation process in a coating machine (Lawes Cota® 07-Manu) [1,21]. For this purpose, the cores were preheated to 45 °C following the suspension application process and maintained under permanent agitation. The temperature and heating time were optimized for this process. After the coating, the solvent was removed by drying. During the core coating process, the weight of 10 tablets was determined every 30min to control the weight gain of the tablets during coating, a procedure adopted as the QbD strategy.

Quality control of the final product

The coated tablets obtained were subjected to quality control pharmacopeial tests [22] and sent for blistering and packaging.

Change control

Owing to the change in the color of the tablets, it was necessary to open the Change Control (CC). Documents requested according to GMP (CHAPTER 4 - DOCUMENTATION) must be prepared for subsequent registration and periodic review of the product [18]. The product goes through a period of stability monitoring for 2 years, with a line batch being permitted instead of a pilot batch,

as this is a minor change in the excipient. For documentation purposes, a comparative table is made with the description of the previous formula and the new formula proposed for the regulatory affairs sector, where at each date of product registration renewal, the protocol with Product Change History (PCH) is sent to inform all changes made to the tablets during this period, in this case, the coating color in 50mg tablets.

Result and Discussion

The best tool for applying QbD is the proposed factorial study covering all the variables inherent to the process. In this case, composition of the coating film, use concentrations, assessment of compatibility between components, process parameters. Before carrying out bench tests, selection and approval by marketing, and the company's management regarding the color of the coating, a risk analysis was carried out, as described by GMP [18]. The risk-management process must be designed and maintained to allow continuous improvement, identification, evaluation, stimulation, and control of the risks associated with products and processes. Risk analysis is a process that involves Critical Quality Attributes (CQA) to ensure that a product has the desired quality according to the CMA [7,8,23].

Failure Modes, Effects and Criticality Analysis (FMECA) are also carried out, which is a process in which a potential failure is analyzed to determine its impacts or effects on the system. In this context, failure must be classified according to severity, which is an activity generally carried out by scoring. FMECA is applied to equipment and production stages, monitoring the impacts of failures on product quality and identifying the elements that make it vulnerable. It is worth mentioning that drug technology involves unit operations that cause a high level of disorder in pharmaceutical materials, therefore, the FMECA practice is an important monitoring strategy [2,10]. The risk analysis in the development of the coating for *Valeriana officinalis L.* 50mg tablets, the target of this research, indicated the technological parameters inherent to obtaining the coating. Failure to weigh the film components, agitation speed of the mixing process, temperature, and heating time during coating and rotation during spraying were the most critical factors, and therefore, those with the highest score on the risk scale, as previously described in the literature [24,25]. Process validation is one of the requirements of GMP [18]. All the unit operations were validated to ensure that the performance was compatible with the technical requirements of the product. Therefore, the QbD strategy is the best solution for improving the quality of pharmaceutical products based on the knowledge of CMA and CPP [10].

Thus, the project to develop *Valeriana officinalis L.* 50mg tablets included direct compression technology, following the unit operations: weighing the powders (calibrated balance), comminution (ball mill), particle size calibration (sifting sieve), mixing the powders ("V" mixer), compression (compressor machine), coating the cores (coating machine), and drying (stove), as illustrated in the following scheme (Figure 1). Some parameters were closely monitored to validate the operation of each unit. The scale was calibrated during the weighing stage. The time and mechanism for particle size reduction were established according to the defined size, 0.25mm, normalized on a sieve with a calibrated mesh. In the mixing stage, the "V" mechanism is adopted because it is more efficient in achieving a perfect mixture [1]. The pharmaceutical ingredients presented satisfactory flow and compressibility properties, which is why direct compression has been applied [11,21]. The filling cam (feeder) was defined according to the density and size of the tablet. An oval-shaped pair of punches was maintained for the *Valeriana officinalis L.* tablets (50mg), as recorded for the 100mg tablets. The height of the lower punch was adjusted to the final weight of the tablet, and the compression force of the upper punch was adjusted to ensure its integrity and mechanical resistance, which was established at 8 tons. It is worth mentioning that all equipment used is made of 316 L stainless steel (low carbon content), compatible with pharmaceutical materials as described in the pharmacopoeia [26]. The cores of *Valeriana officinalis L.* tablets (50mg) were heterogeneous in color, with a brownish-brown tone resulting from the mixture of excipients with the dry extract. The macroscopic appearance of the core indicates a smooth, uniform texture and oblong shape, as previously defined by the punch (Figure 2).

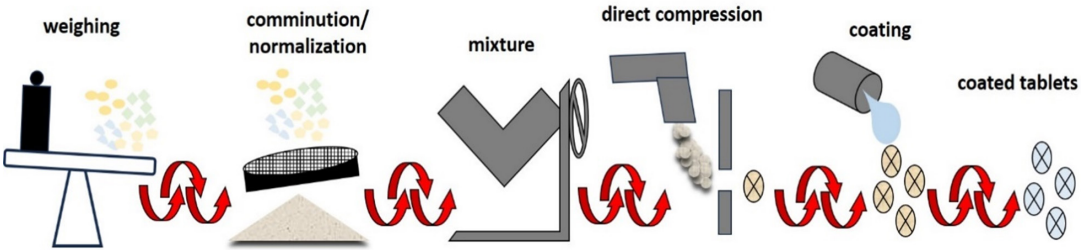

Figure 1: A representative scheme of unit operations was validated for coated tablets of *Valeriana officinalis L.* 50mg.

Figure 2: Illustrative photograph of 50mg of *Valeriana officinalis L.* core.

During the production of the cores, in-process control was performed to evaluate the weight, hardness, and friability. Twenty cores were randomly selected during the compression process to evaluate their weight. The average experimental weight (200.04mg) indicated a variation limit of up to±7.5% on the individual weight of the tested units, according to the pharmacopoeial specification [26]. Analysis of individual results (Table 1) indicates all cores weigh between 185.03mg and 215.04mg, approved this test. Among the tests to check the mechanical resistance of the cores, hardness was checked in 10 units. As it is an informative test [22], the industrial company standardized the limit between 7.00kgf and 12.00kgf as its own specification. The tested units presented a minimum of 7.95kgf and a maximum of 11.82kgf, indicating adequate hardness control for the cores. The individual results for the 10 units tested are listed in Table 2.

Table 1: Results of the weight determination test of *Valeriana officinalis L.* 50mg cores.

Unit	Weight (mg)	Unit	Weight (mg)	Unit	Weight (mg)	Unit	Weight (mg)
1	210.7	6	204.0	11	204.1	16	194.0
2	204.9	7	204.8	12	193.7	17	191.4
3	193.7	8	204.6	13	202.6	18	196.4
4	204.0	9	205.8	14	192.1	19	196.3
5	208.7	10	201.4	15	195.3	20	192.3
Average							200.04

Table 2: Results of the hardness test of *Valeriana officinalis L.* 50mg cores.

Unit	Hardness (kgf)	Unit	Hardness (kgf)
1	9,07	6	7,95
2	11,52	7	11,01
3	10,60	8	10,30
4	8,66	9	8,87
5	11,82	10	10,50

Even though *Valeriana officinalis L.* tablets (50mg) are coated, it is important to evaluate the friability of the core as a complementary test to verify mechanical resistance. To do this, 20 units were accurately weighed and subjected to 100 rotations on the friability test instrument. The generated powder residues were removed and the tested units were reweighed. This batch of *Valeriana officinalis L.* 50mg cores showed 0.05% powder loss and acceptable friability according to the pharmacopoeial specification (<1.5%) [26].

The results of tests evaluating the mechanical resistance, hardness, and friability confirmed the adequate physical integrity of the cores. For tablets, this attribute is critical and directly affects the composition of the master formula and operational parameters of the compression process. The mechanical strength of tablets is a Critical Quality Attribute (CQA) in QbD and is related to the stability and biopharmaceutical performance of the drug product. The use of colored coatings on tablets is a technological strategy adopted for specific purposes, such as the photoprotection of unstable nuclei in the presence of light, standardizing the color of tablets, and differentiating pharmaceutical specialties [27-29]. According to the QbD strategy for changing the color of the coating on *Valeriana officinalis L.* 50mg tablets, four colors were tested: white, yellow, green, and blue (Figure 3), and presented to the board and the marketing sector.

Figure 3: Final appearance of *Valeriana officinalis L.* 50mg tablets after coating with the tested colors.

The shade of blue was chosen because it presents satisfactory pharmaceutical and sensory characteristics (tranquility and calm) for the coating of 50mg tablets of *Valeriana officinalis L.* A homogeneous suspension for coating was obtained, light blue in color, opaque, with a fine texture and medium viscosity, which presented pharmacotechnical properties suitable for the proposal, mainly film formation (Figure 4). The temperature control and heating time during the coating process are CPP, while the thermal stability of the ingredients and drying for adequate film formation are CMA [7,8]. Therefore, a protocol was optimized to properly control the temperature and heating time. The coating process started at 45 °C at 0, 5, 10, and 20min, increased to 47 °C at 30 and 40min, and remained at 48 °C at 50, 60, 90, 120, 150, and 180min. After coating, the cooling process began and was maintained

under agitation, with a temperature reduction of up to 27 °C, and the process was completed. This protocol scheme is illustrated in Figure 5, and the coating process of the *Valeriana officinalis L.* 50mg cores in manufacturing showed system suitability, as observed for the internal part of the coating machine (Figure 6).

Figure 4: Suspension obtained for coating *Valeriana officinalis L.* 50mg cores.

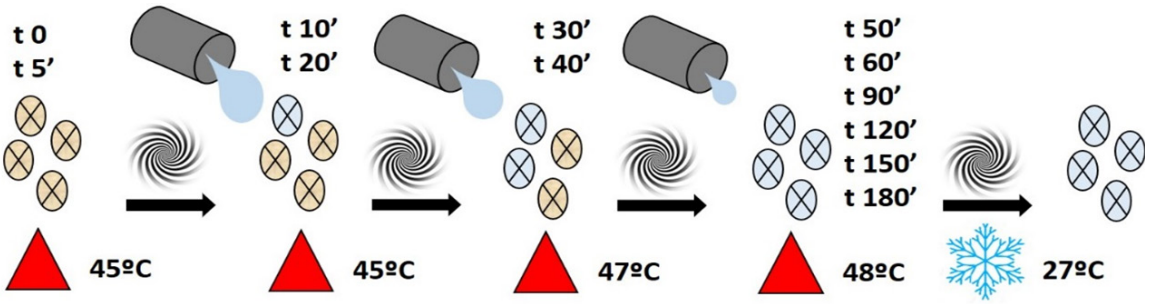

Figure 5: Protocol scheme of optimized temperature and heating time during the coating stage of *Valeriana officinalis L.* 50mg cores.

Figure 6: Illustrative photo of the internal part of the coating machine in the manufacturing of *Valeriana officinalis L.* 50mg tablets.

The film-coating process involves a balance between the amount of suspension to be applied, its drying, uniformity, and complete distribution over the surface of the cores 1. During the tests developed for *Valeriana officinalis L*. 50mg, initial problems were found, resulting in tablets with a rough "orange peel" appearance. This occurred because of the adhesion of the tablets in the coater bucket. At the beginning of the coating application, there was a drop in temperature owing to the cold coating being sprayed onto the hot cores. Other factors that cause tablets to adhere are related to the rotation speed of the coater and high coating application force (exhaustion). These parameters were monitored and controlled using QbD strategies to obtain the final product. The *Valeriana officinalis L*. 50mg tablets coated with the blue suspension showed covering and stability, completely and evenly coating the cores (Figure 7), showing adequate differentiation from the *Valeriana officinalis L*. 100mg tablets coated with the green film. As requested by the industry board, *Valeriana officinalis L*. tablets were obtained in two commercial presentations, 50mg and 100mg, which were visually distinct.

Figure 7: Coated tablets of *Valeriana officinalis L.* (50mg) were obtained on a pilot scale after blue coating was chosen by industry management and marketing.

The pharmacotechnical development sector has established that, for the complete coating of *Valeriana officinalis L*. 50mg cores, the theoretical weight gain of the tablets cannot exceed 10%, therefore the weight of the tablets can reach 220.4mg after coating, a Since, the average weight found for the cores was 200.04mg. The weight increase of the tablets was controlled by using 20 randomly sampled units. The results of determining the weights of the tablets after coating are presented in Table 3. It should be noted that the tested unit has a higher weight than estimated. As it is a parameter with the company's internal specification, and the deviation is higher, there is no criticality in this result. Another pharmacopeial test was conducted to evaluate disintegration. For this purpose, six randomly sampled tablets were subjected to repetitive immersion in an aqueous medium, as described in the method. All units tested showed complete disintegration in 7´12´, in accordance with the specification (<30min) [22]. The type of coating can affect disintegration time [30]. For *Valeriana officinalis L*. 50mg tablets, the soluble coating did not affect the disintegration of the units, which confirms the adequate development of this proposal. The coating process must be carried out to obtain coated tablets that present less variation in weight, size, and shape in relation to the core. The coating must be thin to avoid masking imperfections in the cores caused during the compression process [11,21]. Coated tablets with an adequate texture were obtained without compromising the physical appearance of the cores.

Table 3: Results of the weight determination test of Valeriana officinalis L. 50mg coated tablets.

Unit	Weight (mg)	Unit	Weight (mg)	Unit	Weight (mg)	Unit	Weight (mg)
1	217.9	6	218.3	11	218.6	16	220.0
2	218.6	7	220.4	12	215.9	17	221.0
3	215.8	8	220.1	13	216.2	18	228.8
4	216.1	9	221.5	14	218.4	19	218.5
5	218.1	10	217.7	15	220.3	20	214.4
Average							218.8

Conclusion

Film coating is a complex process because it involves some critical parameters. The results obtained will provide a commercially attractive appearance to the tablets, as well as offer greater stability, being one of the coating techniques most used by the industry. The blue film coating provided complete and uniform

coverage to mask the heterogeneous and dark color of the cores of *Valeriana officinalis L*. (50mg), which also provided adequate differentiation between the 50mg and 100mg doses. The proposed coating in different colors will assist in the blistering process, preventing possible deviations in production and in clinical practice for the patient. QbD strategies, with the definition of CQA, CMA, and CPP, are very useful in the context of pharmaceutical quality systems.

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Author contributions

Emilly Lorrane Fonseca de Souza: Formal analysis; Roles/Writing - original draft. Adriana Nascimento Sousa: Investigation; Visualization. Wagner da Nova Mussel: Data curation, Investigation, Methodology, Roles/Writing: Original Draft. Maria Betânia de Freitas-Marques: Conceptualization; Data curation, formal analysis, Investigation; Methodology; Validation; Visualization; Roles/Writing, and original draft.

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