



# Quality Deviation Handling on the Polymeric Coating of Pharmaceutical Tablets

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## Abstract

**Purpose** This work aimed to map and discuss tablet-coating choice, quality deviations of this process, and corrective actions taken by Research and Development (R&D) teams from pharmaceutical industries.

**Methods** A cross-sectional study of polymeric film coating was conducted in Brazil: a questionnaire based on literature information was sent to R&D divisions from several different companies that produce coated tablets in the country, which focused on the main type of coating systems used, most common quality issues, corrective action to each nonconformity, and the main influences in the choice of the coating system.

**Results** The most used film coating systems are hydroxypropylmethylcellulose + Polyethylene glycol (HPMC/PEG) and polyvinyl alcohol + PEG (PVA/PEG), and the most common non-conformities are orange peel, picking sticking, chipping, and peeling. The main suggestive corrective actions include temperature control, pan speed, spray, and pressure rate. All results were analyzed by us according to literature and authors' expertise. Finally, stability was the main factor that influences the selection of a coating system.

**Conclusion** These data brought knowledge on routine industrial practices, when real deviations happen and matter, with no reports found in the literature.

**Keywords** Film coating · Tablets · Quality control · Pan coater · Troubleshooting

## Introduction

Apothecaries started to sugar-coat tablets in the 1800s to increase the palatability of bitter drugs and protect the medicine from moisture and light. However, this process requires a prolonged processing time and delivers a heterogeneous product with increased risk of microbial contamination, among other disadvantages. Polymeric films are progressively replacing sugar coating since 1954, with the benefits of reducing the time of automated processing and achieving a more uniform coating, in addition to the variety of functions and colors [1–3]. Film coatings can provide drugs protection from

mechanical stress and moisture, odor and taste masking, modified release profiles, better stability, and lower or abrogated gastrointestinal tract irritation [4].

Coating forms when a solution/dispersion of polymer and plasticizer excipients are sprayed on tablets, followed by solvent evaporation and polymer chain coalescence, leading to its adherence on the surface of the tablet. The interaction between polymer and tablet surface relies on hydrogen bond formation and some dipole-dipole and dipole-induced dipole interactions [5]. In addition, the plasticizing agent reduces polymeric intermolecular forces, consequently decreasing its glass transition temperature to a more elastic and adherent film [3]. Surfactants can be added to improve substrate wettability and make it more adherent, or stabilize suspensions and provide emulsion of water-insoluble polymers. Other optional additives are colorant class (dyes and pigments), used, for example, for decorative, discriminative and drug stability purposes; flavoring, anti-adhesives, and pore-forming agents [1, 3, 6].

The coating process is a complex operation with a high number of variables and hard-to-predict outcomes. Therefore, many quality issues may arise if a strict process control is not implemented, ideally being based on quality

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by design [7, 8]. This operation is traditionally performed in pan coaters (Fig. 1), but spray dryer and fluidized bed equipment also coat particles. For this study, we will focus on pan coating parameters.

Non-conformities at the coating stage affect product esthetics and/or functionalities such as the drug release profile, compromising the patient's treatment [9]. Considering the several quality issues faced by pharmaceutical companies in the industrial coating process, the lack of research focused on the industrial frequency of failure types and corrective actions; this study aimed to map and discuss expert opinions from industrial R&Ds teams on the subject. Since manufacturing practices may change due to cultural enterprise practices or regional guidelines and regulations, we focused on our country, Brazil. As evidence of the country's relevance, the pharmaceutical Brazilian market exceeded \$ 16.8 billion in medicine sales in 2016, with 12,798 presentations (corresponding to 6300 products) sold by 214 companies. Among the 20 most commercialized pharmaceutical products in the same year, 17 are drugs formulated mainly in uncoated (41%) and coated (29%) tablets [10, 11]. Additionally, all top 20 companies with the highest revenue in Brazil commercialize coated tablets, except for the Butantan Institute, which is a public company that manufactures vaccines and antivenoms.

## Methodology

This survey research was designed as a cross-sectional study to evaluate the most common polymers, failures, and practices of the coating process. The evaluation instrument was a

questionnaire (Table 2) composed of four questions with on-line access through a website (SurveyMonkey 2018). The subjects of the study were Research & Development (R&D) experts from pharmaceutical companies that manufacture tablets in Brazil. The survey link was sent by email to 29 pharmacists of different pharmaceutical companies that produce tablets, without linking them or their company with the answers. The questions were based on commercially available blends, scientific literature reports and review of defect types, and expertise of the authors on the subject.

According to Sindusfarma Annual Report 2017, there are 446 industries in the country (considering all pharmaceutical medicine for human use, including vaccines); the most concentrated poles are São Paulo (180), Rio de Janeiro (55), Minas Gerais (44), and Goiás (43). The questionnaire was thus sent to the pharmaceutical industrial poles: São Paulo, Rio de Janeiro, Goiás, Minas Gerais, in addition to the states of Paraná, Santa Catarina, and Bahia.

The results were quantitatively evaluated as absolute frequency of responses. The qualitative results were evaluated according to the author's expertise, scientific literature, and industry whitepapers, structured with Ishikawa diagram or topic discussions (Table 1).

## Results and Discussion

According to Close-Up International (data not published), Brazil has 133 pharmaceutical industries selling coated tablets. Considering this number as the highest possible for local manufacturing, at least 12% of manufacturers with R&D in

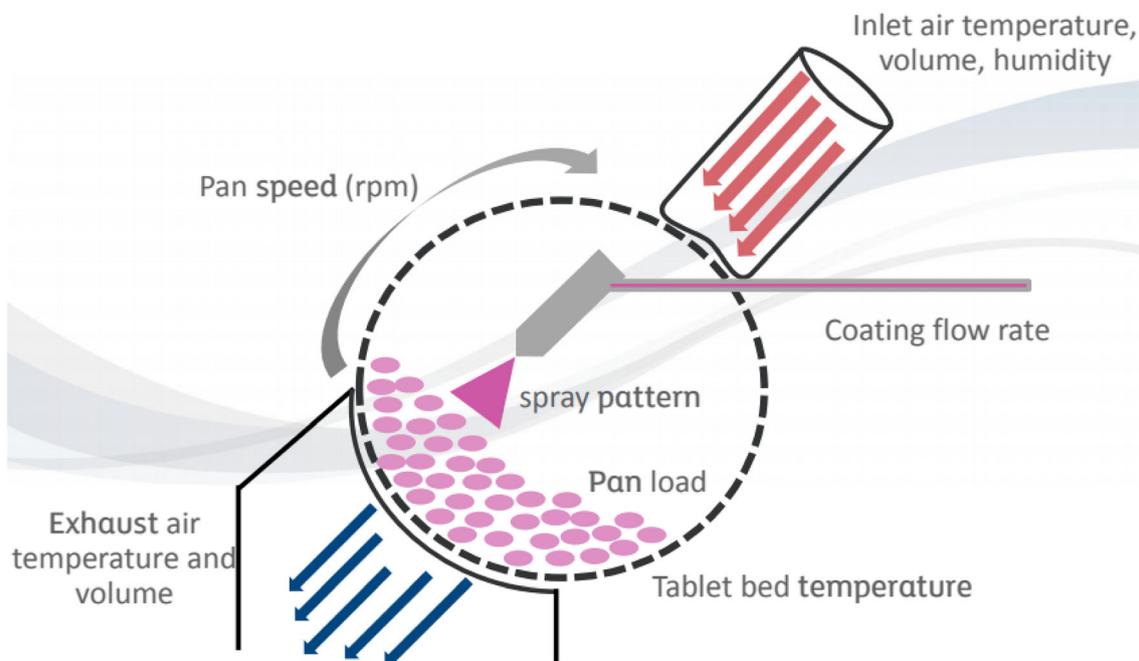


Fig. 1 Scheme of a perforated pan coater, main characteristics, and some process parameters (reproduced with permission from Kerry Inc. 2018)

**Table 1** Questionnaire applied to the technical survey on film coating systems**Question 1. What are the most common types of coating systems in your company products? Check the number of options you need.**

Hydroxypropylmethylcellulose (HPMC / Hypromellose) + Polyethylene glycol (PEG / Macrogol)

HPMC + PEG + Titanium dioxide

Polyvinyl alcohol (PVA) + PEG

HPMC acetate succinate (enteric)

HPMC + Ethylcellulose (EC)

HPMC with lactose, polydextrose or starch

HPMC phthalate (enteric)

HPMC + PVA

HPMC + Hydroxypropylcellulose (HPC/Hiprollose)

Copolymer of methacrylic acid (enteric)

Others (specify)

**Question 2. What are the defects that most occur in the coating process, in your experience? Check the number of options you need.**

Picking sticking (detachment due to adherence between tablets)

Pitting (holes that form without core exposure)

Blushing (whitish spots)

Infilling (coating deposit in embossed printing)

Bridging (formation of a membrane between the ends of low relief printing)

Blistering (local detachment of the bubble-forming coating)

Cratering (craters that expose the surface of the tablet)

Chipping (Chipped or crushed coating, usually on edges)

Blooming (opaque coating)

Color variation

Orange peel (rough appearance)

Mottling (presence of lighter or darker points)

Cracking (Small, thin cracks on top or bottom)

Peeling (Desquamation of the film, loss of adhesion)

Other (please specify)

**Question 3. What were the actions taken to solve the problems marked above? Example: In “color variation”, new coating layer is applied.**

Question 4. What influences the choice of a coating system for a new development? Rank options by importance.

Reference drug or based on another product on the market

Compatibility of the development product with the coating system

Product stability

Easy preparation and application process

Consumer acceptance

Cost

Availability in company inventory (regular sales option)

Brazil answered the questionnaire (17 respondents). We were not able to evaluate the exact sample size significance of the study because the total amount of companies manufacturing coated tablets in Brazil was not available, only the ones selling it (with possible outsourcing involved). Considering the

national ranking of Pharmaceutical Companies with the highest revenue in 2016, 6 of the top 10 were included in this survey, which indicates a high representation of this economically important group.

## Frequency of Coating Types

Hydroxypropyl methylcellulose with polyethylene glycol (HPMC/PEG) stood out as the most frequently used choice of coating for tablets in the studied companies, with almost a quarter of total citations (Fig. 2). It is an esthetic coating, with mechanical protection and low protection against moisture. The HPMC/PEG with titanium dioxide (TiO<sub>2</sub>) was the second most frequent (21.74%), with the same function as the first one, in addition to the white color. TiO<sub>2</sub> containing films can also protect the drug from light-induced degradation, depending on its concentration and the thickness of the resulting film [12]. The HPMC presents a similar molecular curve shape of PEG, conferring a good polymer-plasticizer blend, which gives a better mobility for film coating, aside from the lower crystallizing temperature [13]. In addition, the flexibility to choose alcohol or water as a solvent and low temperatures of the application allows this system to be used in different medicine formulations. Ethanol makes this industrial process easier, with shorter drying periods, but water is the preferred option due to environmental concerns and also only when moisture is not a problem for the substrate [14].

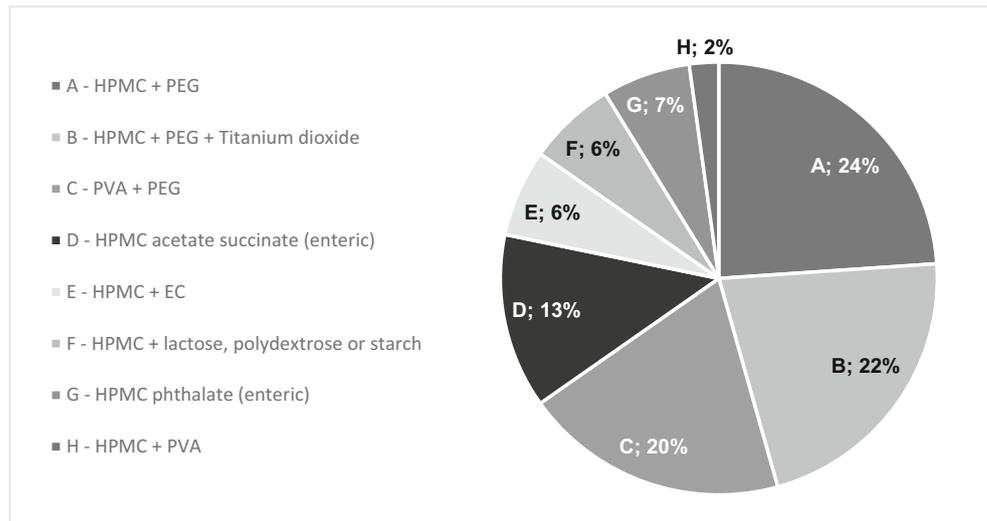
The third most voted coating was the aqueous-based film polyvinyl alcohol with Polyethylene glycol (PVA/PEG). It is an esthetic coating with slippery appearance, mechanical protection and increased protection against moisture. The PVA polymer is biodegradable, has good strength, and confers uniform coatings with increased film adhesion in different formulations. The PEG, besides enhancing film flexibility on its own, together with PVA increases water solubility and swelling [15]. Nonetheless, higher application temperatures restrict its use.

Extended release coatings appeared at a significantly smaller frequency. The enteric coating based on the copolymer of methacrylic acid is the most common one (4th most voted), which provides delayed release upon its dissolution in the basic pH of the intestine. There are also several commercial presentations that facilitate its use: aqueous dispersion, water-dispersible powder, and concentrated solution in organic solvent.

The mix of two polymers to increase film performance appears as less common, with 3 representatives: the HPMC with hydroxypropyl cellulose (HPMC/HPC), making a stronger film with more adhesion; the HPMC with PVA has the benefits of both polymers, such as lower application temperatures and moisture protection; the HPMC with Ethylcellulose (HPMC/EC) provides delayed release due to insolubility of the EC.

The other film coatings cited were the copolymers based on 2-dimethylamino ethyl methacrylate, methyl methacrylate and

**Fig. 2** Frequencies of the most commonly used types of coating systems in the company of the respondent (17 answers, 46 entries). Participants could mark as many options as they feel adequate



n-butyl methacrylate with enteric function. This answer was not considered because it is a polymer and not a coating system.

The options that did not have any votes were HPMC with sugar or starch to decrease costs, and enteric coatings with acetate succinate and phthalate, which are more expensive, but have better performance. HPMC with sugar probably was not voted because this system decreases the coating protection against moisture and this is not desirable considering a tropical country.

### Frequency of Quality Deviation Types in the Industrial Coating Process

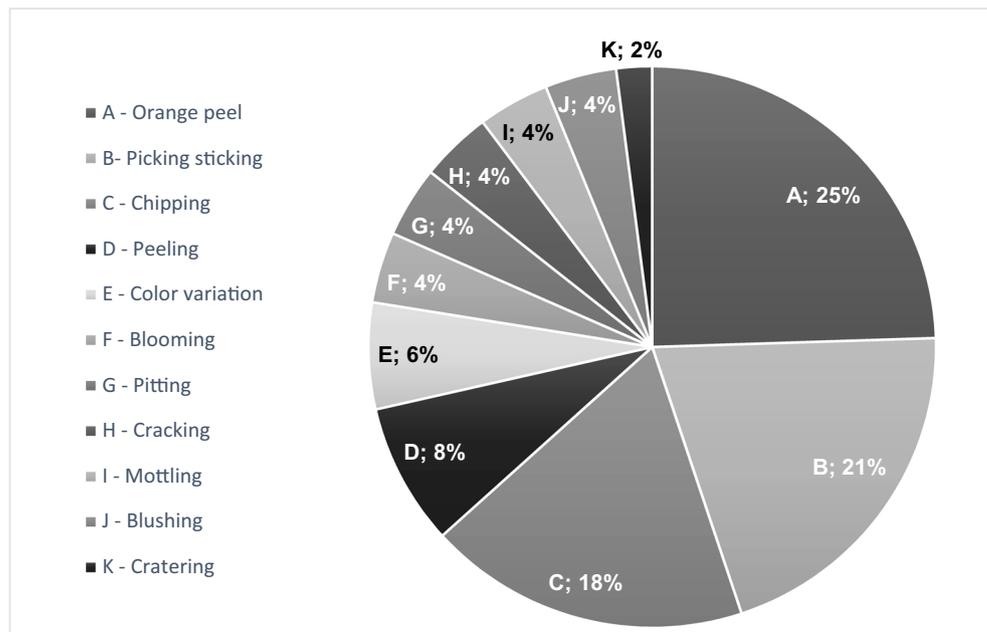
The results of the second question showed that more than 60% of the main defects encountered in the coating process are orange peel, picking, and/or chipping (Fig. 3). All of them

are illustrated in Fig. 4a. The peeling and color variation problems are also relatively common, and others that also occur less frequently are blooming, pitting, cracking, mottling—the presence of lighter or darker points, blushing—whitish or frosted stains, and cratering—holes exposing the surface of the tablet. Peeling, cracking, and mottling are illustrated in Fig. 4b. The non-voted defects and, therefore, not commonly found, were bridging, infilling, and blistering. The results of this question will be discussed in the next question concerning the proposed solutions.

### Quality Deviation Handling

The third question was related to what corrective actions were undertaken by the professionals to solve technical

**Fig. 3** Frequency of the most common non-conformities in the company of the respondent (17 answers, 49 entries). Participants could mark as many options as they feel adequate



**Fig. 4** **a** From left to right: red tablets with orange peel effect, yellow tablets with picking sticking effect, blue tablets with chipping effect. **b** From left to right: white tablets with peeling effect, rose tablets with cracking effect, white tablets with mottling effect (reproduced with permission from Kerry Inc. 2018)



problems. The solutions were related to the problems marked by them in Table 2; the four most common non-conformities are further discussed.

According to the literature, orange peel can be related to the excess of evaporative rate, spray atomization and variation in droplet size, and it influences the esthetic appearance and has the potential to change drug release [3, 6]. Most of the experts proposed actions to solve this problem in accordance with previous reports, except by the increase in pan speed and addition of a new coating layer. Increasing pan speed may not solve the problem, as it is not a problem of homogeneity or moisture, for instance. On the other hand, the addition of a new coating layer could change the properties of the tablet by changing the enteric release of the drug, as an example.

On the contrary, picking/sticking can occur due to an inadequate drying rate and poor spray distribution, among other causes [3, 16]. In this case, increasing pan speed could help improve the tablets drying and avoid making them stick to each other. The most cited actions to solve this issue were adjusting pan speed and temperature. The literature also suggests the calibration of spray guns to certify a uniform spray distribution, aside from adjusting batch size [3]; however, batch size modification involves much more than just the coating step.

Chipping is an issue mainly related to formulations (high tablet friability, film coating with poor mechanical strength), and due to coating process itself (erosion due to too high pan speed and insufficient spray rate) [3]. The experts proposed actions to solve/avoid chipping related with adjustments on these parameters, but some of them might not be efficient, such as reducing coating application (which could diminish the coated area and easily expose the core) and increase pan speed (which could increase tablet attrition).

Regarding peeling, the answers obtained were the most intuitive ones. Nevertheless, reformulation of tablet cores and coating systems might be needed to overcome this issue, action not reported by the respondents [3, 17].

Figure 5 presents the most cited actions to solve the coating issues mentioned. More than 60% of the actions were related to the pan speed, temperature control, flow/application rate, equipment parameters, and application of new coating layer.

It is known that unsatisfactory film coatings can be the result of a poor tablet exposition to the coating liquid, which is related to the time of exposure to the spray within each spin and the number of times the tablet passes through the spray zone. These parameters are directly influenced by pan speed and size, as well as the amount and size of tablets [18]. In the survey, all the main non-conformities had at least one solution related to the control of pan speed, showing that this parameter is well known and must be well controlled to avoid any problem in the coating process.

Temperature control and setup are also conditions to achieve good film formation, as it influences solvent evaporation rate and film appearance [19]. The control of temperature or drying temperature was presented as a solution for orange peel, picking, chipping, blooming, pitting, and blushing. Inlet air temperature is the most important factor of this parameter, due to the high-risk impact in the process, causing drying and resulting in roughness, or increase in moisture, resulting in twinning [6].

Non-conformities can also be a result of poor spray quality of the solution applied on the surface of the tablet. Spray quality is determined by several factors, such as air and liquid velocity, liquid viscosity, atomizing air pressure, shaping air pressure, coating supply rate, nozzle exit orifice diameter, gun-to-bed distance, air-to-liquid mass ratio, and polymer concentration on spray characteristics [19]. Some solutions related to it were “reduce coating application,” “increase

**Table 2** Actions taken by respondents for the most common non-conformities (15 answers)

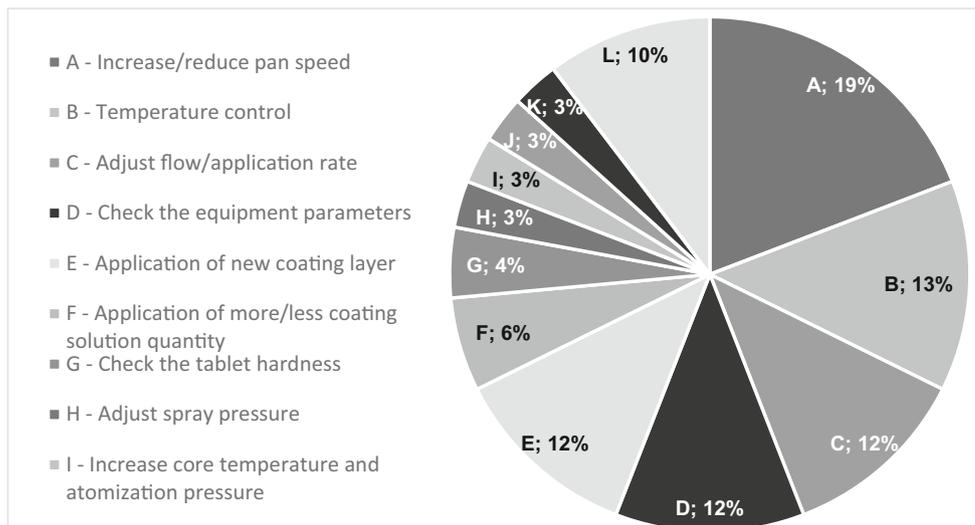
Deviation	Proposed action
A. Orange peel	<ol style="list-style-type: none"> <li>1 - Adjust flow and spray pressure</li> <li>2 - Increase core temperature and atomization pressure</li> <li>3 - Increase pan speed and decrease application rate</li> <li>4 - Check equipment parameters and apply a new coating layer</li> <li>5 - Decrease temperature or solids percentage in the suspension</li> <li>6 - Discard the lot; adjust temperature control and tablet gun-to-bed distance for the next batch</li> </ol>
B. Picking/sticking	<ol style="list-style-type: none"> <li>1 - Increase core temperature and atomization pressure</li> <li>2 - Review coating parameters</li> <li>3 - Control the temperature and apply a new coating layer</li> <li>4 - Increase pan speed</li> <li>5 - Visually review the batch and select the tablets</li> <li>6 - Check the equipment parameters and application of a new coating layer</li> <li>7 - Decrease the amount of solution applied, increase temperature and pan speed</li> </ol>
C. Chipping	<ol style="list-style-type: none"> <li>1 - Reduce pan speed; if coating does not cover, apply more coating</li> <li>2 - Reduce application and pan speed</li> <li>3 - Visually review the batch and manually select tablets</li> <li>4 - Check tablet hardness, reduce pan speed, increase initial application rate and reduce it later</li> <li>5 - Check equipment parameters and apply a new coating layer</li> <li>6 - Reduce coating application, increase pan speed, reduce drying temperature</li> <li>7 - Have a core tablet with “better” parameters</li> </ol>
D. Peeling	<ol style="list-style-type: none"> <li>1 - Change coating polymer</li> <li>2 - Application of new coating layer</li> <li>3 - Check tablet hardness, reduce pan speed, increase initial application rate and reduce it later</li> </ol>
E. Color variation	<ol style="list-style-type: none"> <li>1 - Adjust flow and spray pressure</li> <li>2 - Application of more coating solution quantity and increase pan speed</li> <li>3 - Check equipment parameters and application of new coating layer</li> </ol>
F. Blooming	<ol style="list-style-type: none"> <li>1 - Change coating process parameters (hopper speed, temperature, airflow)</li> <li>2 - Reduce coating application, increase pan speed, reduce drying temperature</li> </ol>
G. Pitting	<ol style="list-style-type: none"> <li>1 - Change coating process parameters (hopper speed, temperature, airflow)</li> <li>2 - Reduce coating application, increase pan speed, reduce drying temperature</li> </ol>
H. Cracking	<ol style="list-style-type: none"> <li>1 - Increase plasticizer and have better evaluation of core tablet parameters</li> <li>2 - Check tablet hardness, reduce pan speed, increase initial application rate and reduce it later</li> </ol>
I. Mottling	<ol style="list-style-type: none"> <li>1 - Apply new coating layer</li> <li>2 - Mill the pigments suspension for a longer time</li> </ol>
J. Blushing	<ol style="list-style-type: none"> <li>1 - Check equipment parameters and application of new coating layer</li> <li>2 - Reduce coating application, increase pan speed, reduce drying temperature</li> </ol>
H. Cratering	<ol style="list-style-type: none"> <li>1 - No action was presented for solutions</li> </ol>

application rate,” “adjust flow and spray pressure,” and “increase atomization pressure.” This parameter has more variables and needs to be controlled to avoid the main non-conformities. Moreover, other studies show that atomization air pressure and spray rate are high-risk factors. Improper air pressure can cause defects such as picking and sticking, due to large droplet size in case of low pressure, and it is

responsible for tablet roughness. The improper spray rate can cause twinning, sticking, and orange peel effect [6].

Other parameters of previous operation units can influence the coating process, such as the force of compression, tablet porosity, excipients, ingredients in the system coating formulation such as plasticizer and colorants, and storage conditions, [7]. This was revealed in the survey, where solutions

**Fig. 5** Most presented actions for solving coating issues



as “evaluate core tablet parameters” and “check hardness of the tablet” were presented for chipping, peeling, and cracking, and “mill pigments suspension for longer time” was suggested for mottling.

Figure 6 presents Ishikawa’s diagram with the critical process parameters during the tablet coating process. The most important parameters related to the responses are highlighted in the diagram: atomization and pattern air pressure, spray rate, temperature, and rotational pan speed. The amount of coating layers is a parameter that was not present in the literature but was frequently considered in the questionnaire.

An important consideration to be made about the orange peel effect, the most common quality issue presented in the study, is that one third of the people who answered the question about this specific problem said that no action could be undertaken to solve it. If the final tablet is orange-peel-like, and if this problem influences the functionality of the drug, the whole batch should be discarded. Another study also shows that tablets with very rough surfaces can interrupt

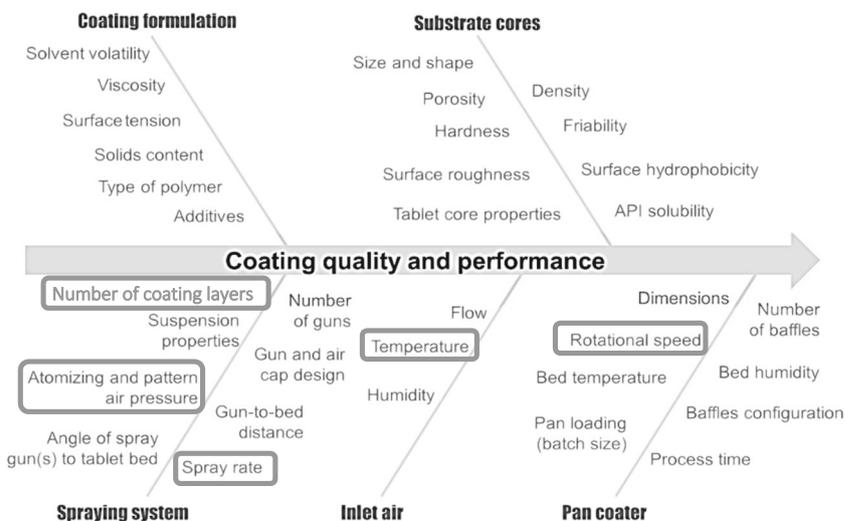
production, as they have high friction and impair transportation in the chutes [19].

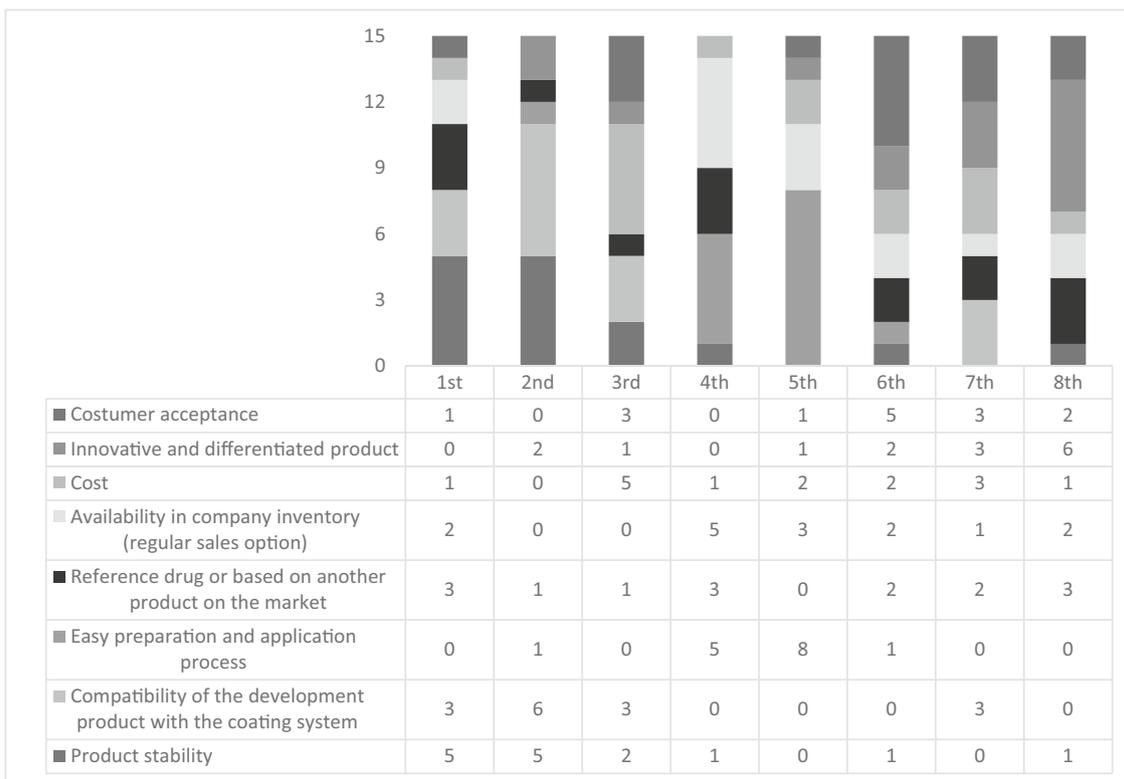
Interestingly, the high amount of answers referring to checking equipment parameters as a solution to coating issues indicates that this is not a well-established step of the coating process. Prior study and determination of these parameters help to reach good quality outcomes. Specifically, the application of the concept “quality by design” - which determines that quality is scientifically designed with product and process characteristics, and is not an attribute evaluated at the end of a process [20] - could avoid waste of time and financial expense, for example, preventing the discard of the whole lot after obtaining orange peel tablets.

**Factors that Influence the Choice of a Coating System in R&D**

The main reasons to choose a specific coating system are product stability and its compatibility with the product

**Fig. 6** Identification of critical process parameters of coating based on scientific literature. The most critical ones as pointed by respondents are highlighted with gray boxes (adapted from [8, 9])





**Fig. 7** The most important parameters for choosing coating system in the company of respondents (15 answers); for this question, eight options were presented to be numbered in order of importance

(tablet), which is also related to stability (Fig. 7). The stability test is required for product registration, which evaluates possible chemical degradation or physical changes of a pharmaceutical product during storage time [11]; it is, therefore, the logical parameter of choice, expected by us to be the main reason. However, some highlighted as most important the coating of a reference drug or other product coatings that are already on the market, an expected parameter in a country with greater development/manufacturing of generics than innovative drugs. Generics were for the first time in 2016 the most commercialized drugs in amount of packages sold, with seven of the top 10 pharmaceutical companies with the highest revenue in Brazil producing them (all 7 responded to this survey) [10]. Choosing a market reference does not exclude stability concerns, but it is expected that what is being sold is stable. Cost, also classified as an important item in the questionnaire, is another consequence of the generic market, in which products should be at least 35% cheaper than the reference product [11].

### Conclusion

Few studies were found regarding the analysis of quality deviations and corrective actions in tablet coating, whereas none

contemplates cross-sectional assessments with pharmaceutical companies. Noteworthy, some of the actions related to solving the issues during this process did not follow what is found in the literature, or even the opposite of the theoretical providences suggested. This indicates that experiences acquired with practical knowledge in the daily work routine are more relevant in the industry than literature reports. For this reason, it is very important to link both industry and literature knowledge to find best and reliable practices for product development and its maintenance during their life cycle, such as having a strong control of higher risk parameters early in the process, and use “quality by design” approaches to prevent these problems. We believe this study will be a valuable tool for new product developments, with industrial or research purposes, to unite useful and non-recommended practices in the pan coating process of tablets.

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### Compliance with Ethical Standards

**Conflict of Interest** In accordance with our ethical obligation as researchers, we are reporting that Erica Costa Fernandes and Nathalia

Rondolfo have an employment relationship with a company that may be affected by the research reported in the enclosed paper. We have in place an approved plan for managing any potential conflicts arising from that involvement.

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