Universidade de Lisboa

Faculdade de Farmácia

PREDICTIVE DISSOLUTION TEST

Tânia Sofia Rodrigues Freire

Dissertação de Mestrado orientada pela Professora Doutora Helena Florindo
e coorientado pelo Doutor Dr. Rui Martinho.

Master of Science Degree in Pharmaceutical Engineering

Public

2021

Predictive Dissolution Test

Tânia Sofia Rodrigues Freire

Dissertação de Mestrado Integrado em Engenharia Farmacêutica apresentada à Universidade de Lisboa através da Faculdade de Farmácia e Instituto Superior Técnico

Orientadores: Prof. Dra. Helena Florindo
Co-Orientadores: Dr. Rui Martinho

2019/2020

RESUMO

Esta dissertação explora o conceito de *Real Time Release* aplicado à dissolução de comprimidos. O objetivo é propor uma estratégia de controlo de qualidade apropriada alternativa para um medicamento, cuja forma farmacêutica é comprimido revestido por película contendo ibuprofeno ativo, através da análise da *guideline* ICH Q6A e outros conceitos regulamentares.

O ensaio de dissolução é dos testes mais relevantes pela indústria farmacêutica em formas farmacêuticas orais, nomeadamente no controlo de qualidade final dos lotes fabricados. O aumento do conhecimento nesta área e a aplicação de métodos de monitorização mais eficientes são fundamentais para a melhoria do processo de fabrico e do seu controlo.

A metodologia envolveu as seguintes etapas: (1) desenvolvimento de análises de risco para identificar os parâmetros que impactam os atributos críticos de qualidade, que constituem ensaios que devem estar dentro de limites apropriados para assegurar a eficácia, qualidade e segurança de um medicamento, do ensaio de dissolução na formulação em estudo; (2) confirmar que os dados apresentam variabilidade suficiente para serem considerados no estudo de avaliação de robustez (3) se considerados suficientes, através de uma análise de robustez, investigar a relação existente entre os fatores identificados no projeto e respetivos perfis de dissolução.

Os parâmetros identificados como possivelmente impactantes da cinética de dissolução são: tamanho da partícula de substância ativa, espessura do revestimento, dureza do comprimido e quantidade de substância ativa. Estes parâmetros são monitorizados em rotina, através de testes realizados durante o processo o fabrico, constituindo, assim, uma das abordagens previstas na *guideline Real Time Release Testing*.

Com base nos resultados obtidos, comprovou-se que, para o medicamento em estudo, é viável eliminar o teste de dissolução das especificações do medicamento em estudo. A confirmação da robustez do processo e da formulação do medicamento em estudo asseguram que o perfil de dissolução tem um comportamento previsível e conforme as especificações.

Palavras-chave: dissolução, desintegração, ibuprofeno, risco, BCS.

ABSTRACT

This dissertation explores the concept of Real Time Release applied to the dissolution of tablets. The goal is to propose an alternative appropriate quality control strategy for medicine, whose pharmaceutical formulation is a film-coated tablet containing active ibuprofen, through the analysis of the ICH Q6A guideline and other regulatory concepts.

The dissolution test is one of the most relevant tests carried out by the pharmaceutical industry in oral dosage forms, namely in the final quality control of manufactured batches. The increasing knowledge in this area and the application of more efficient monitoring methods are fundamental for the improvement of the manufacturing process and its control.

The methodology involved the following steps: (1) development of risk analyses to identify the parameters that impact the critical quality attributes, which consists on those parameters that must be wihtih appropriate limits to ensure the adequate afficacy, quality and safety of a medicine, of the dissolution test in the formulation under study; (2) to evaluate the available data regarding its variability (3) if considered sufficient, through a robustness analysis, to investigate the relationship between the factors identified in the project and the respective dissolution profiles.

The parameters identified as possibly impacting the dissolution profile are: active pharmaceutical ingredient particle size, coating thickness, tablet hardness and amount of active pharmaceutical ingredient. These parameters are already monitored in routine, through tests carried out during the manufacturing process, thus constituting one of the approaches considered in the Real Time Release Testing guideline.

Based on the results obtained, it was proved that, for medicine under study, it's feasible to eliminate the dissolution test from the specifications of the medicine under study. Confirmation of the robustness of the process and the formulation of the medicine under study ensures that the dissolution profile has a predictable behaviour and according to specifications.

Keywords: dissolution, disintegration, ibuprofen, risk, BCS.

AGRADECIMENTOS

Gostaria de agradecer à Generis Farmacêutica S.A., nas pessoas da Dra. Ana Cidra e da Dra. Helena Correia, por me terem proporcionado as condições necessárias ao desenvolvimento desta tese de mestrado e por sempre terem acreditado e investido em mim.

Agradeço também ao Dr. João Lopes, meu professor, à Dra. Helena Florindo, minha orientadora, e ao Dr. Rui Martinho, meu co-orientador, por terem colaborado ativamente na orientação desta tese de mestrado, pela disponibilidade demonstrada ao longo deste tempo e por todo o apoio e conhecimento transmitidos durante a realização deste trabalho.

Gostaria, ainda, de agradecer aos meus colegas e amigos Carlos Santos e Adriana Costa pelo constante apoio, pelas discussões elucidativas e pelos exemplo de empenho e profissionalismo.

LIST OF ABBREVIATIONS

RTRT	Real Time Release Testing
QbD	Quality by Design
CQA	Critical Quality Attributes
TPP	Target product Profile
TPQP	Target Product Quality Profile
CMA	Critical material attributes
CPP	Critical process parameters
GMP	Good Manufacturing Practices
CE	Comissão Europeia
EMA	Agência Europeia do Medicamento
US-FDA	United Stated Food and Drug Administration
FMEA	Failure Modes and Effects Analysis
MAA	Marketing Authorisation Application
Ph. Eur.	European Pharmacopoeia
FP	Finish Product
USP	United States Pharmacopeia
BCS	Biopharmaceutics Classification System
ICH	International Council for Harmonisation
RPN	Risk Priority Number
O	Occurrence
I	Impact
GI	Gastrointestinal
D	Detectability
IPC	In-process-control
PSD	Particle size distribution
NSAID	Nonsteroidal anti-inflammatory drug
Ph. Eur.	European Pharmacopoeia
USP	United States Pharmacopeia
MAA	Marketing Authorisation Application

INDEX

LIST OF TABLES

LIST OF FIGURES

1.

INTRODUCTION

1. INTRODUCTION

1.1. REAL TIME RELEASE

Real Time Release Test (RTRT) is a system that assures the product is of intended quality, based on the information collected during the manufacturing process. This is done through product knowledge and process understanding and its control [1].

On a routine basis, before a medicinal product is released for sale, the Qualified Person should consider, among other data, the conformity of the product to its specification [2]. In the case of approved RTRT, this conformity would not routinely be supported by results of final product testing; instead, information obtained during the manufacturing process is considered for batch release purpose: any failure should be investigated and trending should be followed up appropriately. Batch release decisions shall be made based on the results of these investigations and must comply with the content of the respective marketing authorization and current GMP requirements [3].

The introduction of RTRT requires pre-authorization by the competent authority: it may be introduced as a part of a new application, that is based on an enhanced product, or may be introduced following a variation of an existing market authorization, when more experience has been gained with the manufacture of the product and sufficient product and process knowledge has been demonstrated. In both cases, adequate risk management should be demonstrated in line with the relevant International Conference on Harmonization (ICH) guidelines [3].

The goal of this project is to feasibility of the application of Real Time Release regulatory strategy on a specific medicine, Ibuprofen 600 mg, Film-coated tablet, against the current concept of Quality by Evidence, which means complying with the registered specifications, in this case, for Dissolution Test to support the batch release decision.

Implementation of such systematic approaches in pharmaceutical manufacturing industry would reduce the need to perform tablet dissolution testing, which would improve efficiency in the manufacturing process and time to market capacity.

The following chapters share the interpretation of regulatory requirements, namely those mentioned in ICH Guideline Q6A *"Specifications, Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"*, product United States Pharmacopeia (USP) Monograph and Biopharmaceutics Classification System considering that these guidances/concepts circumscrive, from a regulatory point of view, the concept of dissolution in solid pharmaceutical forms. Taking these requirements into account, the solubility profile of ibuprofen and of the formulation under study will be evaluated and interpreted. The final goal is to conclude about the possibility to eliminate realization of Dissolution Test on a routine basis.

1.2. REGULATORY REQUIREMENTS

1.2.1. Monograph

Conventionally, a medicinal product must routinely comply with the requirements stated in the approved specification for release and shelf-life. As part of the approved specifications for tablet medicines, dissolution test has an important role on the final decision for a batch to be sold in the market: its approval or rejection depend on the similarity or the deviations of the dissolution test to the reference values [4].

Over the past few years, the European Pharmacopoeia (Ph. Eur.) and United States Pharmacopeia (USP) have been elaborating Finish Product (FP) monographs containing chemically defined active pharmaceutical ingredients, applicable to immediate-release solid dosage forms, tablets and capsules. The FP monographs describe a set of specifications and methods, which rational for its definition is based on currently approved medicinal products in European Member States. Individual monographs play a major role in ensuring that medicinal products throughout Europe meet the same quality standards, thereby contributing to patient safety [4]. Nevertheless, the suitability of monograph specifications to adequately control the quality of the finished product needs to be demonstrated in the marketing authorisation application (MAA).

The Dissolution test procedure (test conditions, limits and acceptance criteria), if specified in the monograph, are mandatory unless otherwise stated in the monograph: *"unless otherwise justified and authorised"* [5].

However, this position has been found to be rigid because the dissolution profile may be affected by the formulation and/or the manufacturing process. On January 2019, the European Pharmacopoeia Commission decided that this approach should be reviewed; on November 2020, the European Pharmacopoeia Commission decided that a dissolution or disintegration test will be included in each medicinal product monograph on an immediate-release solid dosage form: *"(…) In line with the relevant guidelines applied nationally or regionally, such as the ICH Q6A guideline, and with the relevant Ph. Eur. dosage form monograph, a suitable product-specific dissolution test has to be proposed by the applicant for routine quality control to confirm batch-to-batch consistency. This test must be described in the MAA for submission to the competent authority, unless there is data justifying the replacement of the dissolution test by a disintegration test. (…)"* [6].

This position reinforces the openness of authorities to apply for one of the tests:

Dissolution Test or Disintegration Test.

1.2.2. Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) is a system to differentiate the active pharmaceutical ingredients based on their solubility and permeability. An active pharmaceutical ingredientsis considered highly soluble when the strength of the highest dose is soluble in 250 ml or less of aqueous media over the pH range of 1.0 to 6.8; high-permeability active pharmaceutical ingredients are generally those with an extent of absorption that is greater than 90% in the absence of documented instability in the gastrointestinal tract or those whose permeability has been determined experimentally. According to the BCS, drug substances are classified as follows and described in Figure 1 [7]:

- Class 1: High Solubility – High Permeability;
- Class 2: Low Solubility – High Permeability;
- Class 3: High Solubility – Low Permeability;
- Class 4: Low Solubility – Low Permeability.

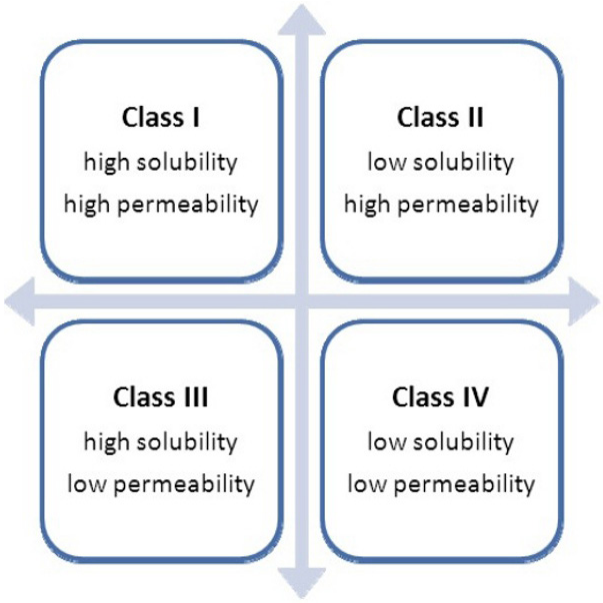


FIGURE 1. Biopharmaceutics Classification System.

In the case of high solubility/low permeability active pharmaceutical ingredients (class III), permeability is the rate controlling step, depending on the relative rates of dissolution and intestinal transit. For low solubility/high permeability active pharmaceutical ingredients (class II), dissolution may be the rate limiting step for its absorption and a good *in vivo - in vitro* correlation can be expected [7].

This classification can be used as a basis for defining specifications of in vitro dissolution and to justify biowaivers: BCS has been implemented for waiving bioequivalence studies based on

the solubility and gastrointestinal permeability of active pharmaceutical ingredient and can be strategically deployed to save time and resources during generic medicine's development [8].

In 2000, the US-FDA was the first regulatory agency to publish guidance for pharmaceutical industry describing how to meet criteria for requesting a waiver of *in vivo* bioavailability and bioequivalence studies for Class I active pharmaceutical ingredient (highly soluble, highly permeable). Subsequently, the World Health Organization (WHO) and European Medicines Agency (EMA) published guidelines recommending how to obtain BCS biowaivers for BCS Class III drugs (high solubility, low permeability), in addition to Class I drugs. In 2015, the US-FDA became better harmonized with the EMA and WHO following publication of two guidances for industry outlining criteria for obtaining BCS biowaivers for both Class I and Class III active pharmaceutical ingredient [8].

The scientific rationale for not granting biowaiver extension for Class II active pharmaceutical ingredient is that their oral absorption is most likely limited by in vivo dissolution. The determining key is then the solubility in the absorbing region of the intestine. This rational suggests a potential to define an intermediate solubility class for active pharmaceutical ingredient that are soluble either in the intestine or in the stomach (different pH conditions). BCS guidance is considered to be conservative with respect to the class boundaries of solubility and permeability. In line with this discussion and other, validity and applicability of BCS have been subject of extensive research and discussion. Thus, several initiatives have been raised, hopping for the revision of BCS classification for additional biowaivers (*in vivo* bioavailability and/or bioequivalence studies not considered necessary for product approval), based on the underlying physiology of the gastrointestinal tract. One of the proposed changes is to add new class boundaries for solubility and permeability, such as an intermediate solubility class for BCS Class II drugs dependant the specific location where the active pharmaceutical ingredient is actually absorbed [9]. This proposal can be useful for pharmaceutical industry, to support them otimizing its control strategies in terms of costs and resources.

1.2.3. ICH Guideline Q6A

From a regulatory perspective, according to ICH Topic Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products published and last developed in year 2000: if below four conditions are fulfilled, Dissolution Testing for immediate release of solid oral medicines may be replaced by Disintegration testing:

1. The dosage form does not exhibit modified release characteristics;
2. The drug has a dose/solubility ratio not less than 250 mL over a pH range of 1.2– 6.8;
3. More than 80% of the dose is dissolved within 15 minutes at pH values of 1.2, 4.0, and 6.8;

4. A relation has been determined between dissolution and disintegration.

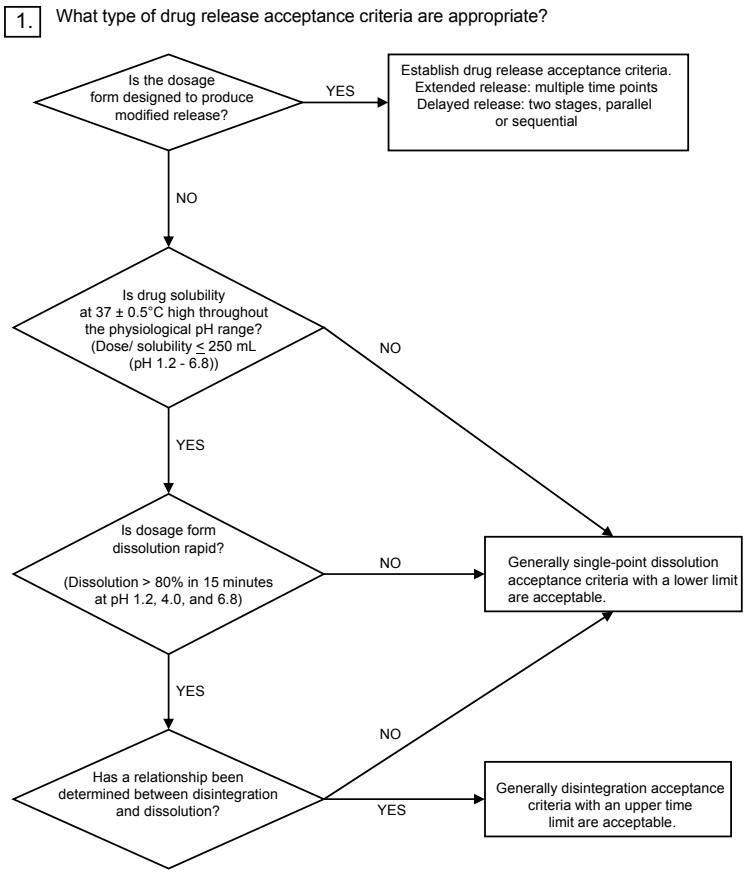


FIGURE 2. ICH Q6A, Dissolution Test tree decision. [4]

According to the requirement 2, regarding active pharmaceutical ingredient solubility, those that are classified with BCS class I and III can have their dissolution testing replaced by disintegration. The main rationale for limiting surrogate tests to highly soluble active pharmaceutical ingredientis related to the fact dissolution profile of tablets are largely independent on the rate of active pharmaceutical ingredient solubilization. Consequently, the overall dissolution profile is dictated by tablet disintegration. For BCS class II and IV products, the active pharmaceutical ingredient dissolution rate is assumed to be a major factor in the overall tablet dissolution. Therefore, disintegration might not be the overall rate-limiting step for low-solubility compounds and cannot be used to ensure consistent release of the active pharmaceutical ingredient from the drug product [10].

In addition to the active pharmaceutical ingredient classification, ICH Q6A predicts two additional requirements: dosage form dissolves rapidly and a relationship has been determined between disintegration and dissolution. However, according to the 2017 guideline *"Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action"* for the last requirement about drug products containing a BCS class I or class III, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes have been made in material specifications and/or manufacturing parameters. In these cases, the method may adequate without further justification or be replaced by a disintegration test [11].

1.3. IBUPROFEN

Ibuprofens chemical name is (RS)-2-(4-Isobutylphenyl) propionic acid and its structure shown in Figure 6.

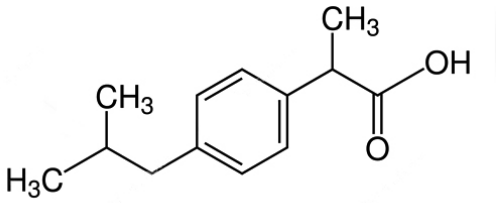


FIGURE 3. Ibuprofen chemical structure. [26]

The molecular weight of ibuprofen is 206.28 and its molecular formula is $C_{13}H_{18}O_2$.

Ibuprofen has analgesic, anti-inflammatory and anti-pyretic properties. The drug's therapeutic effects as a nonsteroidal anti-inflammatory drug (NSAID) are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis. Ibuprofen is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthrosis and other non-rheumatoid (seronegative) arthropathies.

Ibuprofen is a NSAID derived from propionic acid and used widely as an analgesic and antipyretic. It has a pK_a value of 4.5 and is poorly soluble in water (0.078 µg/mL). Ibuprofen is a BCS class II drug: good permeability and low solubility (low solubility at pH 1.2 and 4.5 and high solubility at pH 6.8) [19].

In theory, for BCS Class II drugs, a strong correlation between in vitro dissolution and in vivo absorption can be established if the in vitro dissolution simulates the gastrointestinal tract physiology.

Ibuprofen solubility is pH-dependent, high solubility according to BCS requirements only above a certain pH value. At pH values near neutral, the solubility of ibuprofen is sufficient to comply with criterion for high solubility: a dose/solubility quotient of less than 250 mL. As these pH values are closer to those at the absorption sites in the small intestine, they are therefore more relevant in terms of systemic absorption of ibuprofen [19].

Accordingly, ibuprofen may also fit in the newly proposed "intermediate solubility class" suggested for acids and bases that are highly soluble at either physiologically relevant pH 1.2 or 6.8. Due to this, current publications suggest pH-dependent soluble, highly permeable, weak acidic ionizable drug compounds should be handled like BCS class I Drugs [20].

1.4. DISSOLUTION

Dissolution Testing is performed to verify dissolution of active pharmaceutical ingredients in simulated gastrointestinal fluid, to measure the release performance of the pharmaceutical for absorption. Dissolution testing is an important tool for characterizing the performance of an oral solid dosage form. Its significance is based on the reasoning that for an active pharmaceutical ingredients to be effective, it must first be released from the product and be dissolved in the gastrointestinal fluids before absorption into the bloodstream takes place [13].

For generic medicinal product, the dissolution test is required to ensure, not only the product quality, but also guarantee equivalence from the original product. Hence, the active pharmaceutical ingredients dissolution test becomes more important for the generic process characterization. The absorption of active pharmaceutical ingredients from a solid dosage form after oral administration, depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract [14].

For a commercial product, the dissolution test is routinely used for quality control and for quality assurance purposes, to ensure consistency between production batches, or to support scale-up and post-approval changes made to the manufacturing process. Dissolution test highly consumes time, material, equipment and human resources.

To understand the dissolution process: when tablet is introduced in the water, the tablet disintegrates into granules and the granules further disaggregate into fine particles. Dissolution of the active pharmaceutical ingredients occurs simultaneously with the disintegration process, as it can be verified on Figure 4 [15].

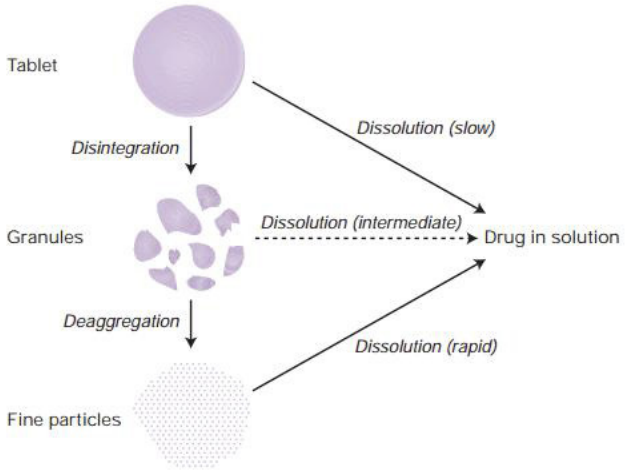


FIGURE 4. Relation between Dissolution and Disintegration test.[12]

The dissolution rate is defined as the rate or speed at which an active pharmaceutical ingredients dissolves in a medium. Dissolution rate of solids in each medium under fixed hydrodynamic conditions is described by the Noyes-Nerns equation [15]:

$$\frac{dC}{dt} = K_1 Cs$$

FIGURE 5. Noyes-Nerns equation.

Where K1 is the intrinsic dissolution rate constant and DC/dt is the intrinsic dissolution rate (mg cm^2/s). The surface area influences the dissolution rate of the active pharmaceutical ingredients; the dissolution rate of an active pharmaceutical ingredients may be increased by increasing the surface area. Therefore, by studying the dissolution rate of an active pharmaceutical ingredients with a constant surface area, the intrinsic dissolution rate (IDR) can be calculated.

According to The modified Noyes-Whitney equation, the dissolution rate is proportional to both solubility and surface area, according to Figure 6 [15,16]:

$$\frac{dC}{dt} = \frac{AD\ (Cs - C)}{hv}$$

FIGURE 6. The modified Noyes-Whitney equation.

Where D is the diffusion coefficient in the dissolution medium; h is the thickness; A is the surface area; v is the volume; Cs is the concentration of the drug at saturated solution; and C is the concentration at particular time, t. [15,16]:

The evaluation of the dissolution rate of an active pharmaceutical ingredients in various dissolution media (variation of pH or use of surfactants) is an indication of the *in vivo* behaviour of the active pharmaceutical ingredients.

There are many factors that can influence the drug dissolution rate, like the active pharmaceutical ingredientsphysicochemical properties (e.g. particle size or solubility, molecular structure, polymorph forms), the formulation composition and characteristics (e.g., excipients, hardness, manufacturing process), and the dissolution method used for its assessment (e.g., apparatus, medium, test conditions, sampling, and sample analysis). Additionally, the dissolution rate can show dependence on the presence of manufacturing variables such as compression force, packaging type, storage conditions and changes in the surface area [17].

Disintegration test is also a standardized test intended to determine the capacity of tablets and capsules to disintegrate at a certain time in certain conditions determined in the pharmacopoeias. A capsule or tablet may disintegrate into smaller particles, but if the active pharmaceutical ingredients do not dissolve, it will not be available to be absorbed in the small intestines [18].

The greater simplicity of disintegration compared with dissolution testing (e.g., no analytics needed, lesser volume of fluids required, less time-consuming) makes the idea of putting more focus on disintegration more attractive. However, this process has disadvantages as it has little reproducibility. As previously discussed, this has been recognized by the ICH that allowed the use of disintegration testing as a surrogate for dissolution testing if certain conditions are met. Therefore, focusing more interest and research on disintegration testing could, because of the test simplicity, enable the pharmaceutical companies to save appreciable expenses in terms of time, efforts, and even money.

Ibuprofen formulation under study is robust and consistent: it has been on market for more than 10 years. It's manufacturing process regards humid granulation and it counts with following excipients:

Core: lactose monohydrate, maize starch, hypromellose, microcrystalline cellulose 102, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.

Coating: Opadry (aqueous film coating) and water.

For the medicine under study, the target sites of active pharmaceutical ingredient absorption are the jejunal parts of the small intestine, which pH is 7 to 9.

The USP monograph for ibuprofen tablets dissolution test (reference is made do **Annex 1**) predicts to measure the percentage of dissolved ibuprofen in 900 mL phosphate buffer pH 7.2 at 50 rpm using the paddle apparatus. The specification for compliance is not less than 80%

(Q) of the labelled amount of $C_{13}H_{18}O_2$ is dissolved in 60 minutes [21].

Being ibuprofen highly soluble at pH 7.2, it is expected that medicine under study fills unequivocally the third ICH Q6A requirement: dosage form is rapidly dissolved (dissolution > 80% in 15 minutes). This assumption can be confirmed by analysing the dissolution data of 5 subsequent batches of medicine under study (Figure 7).

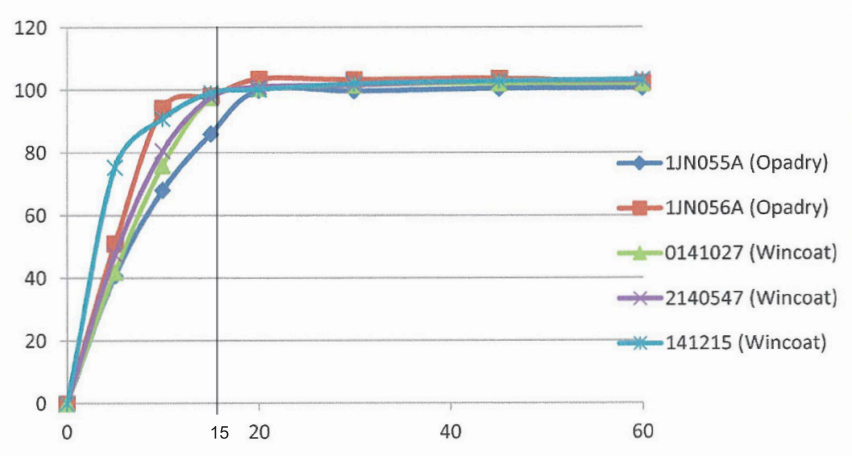


FIGURE 7. Dissolution profile of 5 subsequent batches of medicine under study.

2.

DOSAGE FORM DISSOLUTION PROFILE ANALYSIS

2. DOSAGE FORM DISSOLUTION PROFILE ANALYSIS

2.1. GENERAL APPROACH

Having confirmed that first, second and third requirements, stated on ICH Q6A Decision tree regarding Dissolution Test, are filled by ibuprofen medicine under study, this study section intends to evaluate compliance with last requirement: For that, the following criteria needs to be evidenced and discussed for compliance: Has a relationship been determined between disintegration and dissolution?

The defined strategy to answer the above question will be the following:

- **Risk assessment:** via Ishikawa diagram and FMEA (Failure Mode and Effects Analysis), to identify the parameters that characterize dissolution of medicine under study, i.e., those parameters whose variability, in routine, may have higher impact on its dissolution profile. This knowledge will be obtained through the analysis of data recorded during medicine development process, process validations and overall experience for the last 10 years (time in the market). All information will be integrated and evaluated, thanks to the incorporation of risk analysis methodologies.
- **Critical Quality Attributes Data Compilation:** data from 58 batches manufactured for the last 2 years (reference is made to **Annex 4**) will be collected (analytical results and manufacturing parameters) for the process parameters identified as possibly being critical for dissolution profile;;
- **Data variability assessment:** a statistical study will be adopted in order to assess if the available data has enough variability, thereby confirming, if it is enough to proceed with assessment of existence of a mathematical relation between Disintegration Time, or any other parameter, and the Dissolution test;
- **Relation between Critical Quality Attributes and Dissolution analysis:** Study the relation between process parameters and data from the with Dissolution test.

These steps will be discussed in more detail in the following sections.

This study presents a stepwise approach to study the Dissolution Test of an existing product, which has been manufactured at industrial scale for more than 10 years. Documentary records of 58 batches produced for the last 2 years of production (reference is made to **Annex 4**), during 2018–2019, were chosen as they represent the current manufacturing process of the medicine under study: the equipment and facilities used are common to all 58 batches. Also, during the mentioned period, no significant change control was registered for the established manufacturing process.

2.2. RISK ASSESSMENT

Risk assessment is a valuable science-based process in quality risk management that supports the process of identifying material attributes and process parameters that could potentially influence on product Critical Quality Attributes (CQAs) such as Dissolution [22, 23]. A comprehensive risk assessment was undertaken to identify process parameters whose variability may influence the Dissolution test of conventional, immediate-release tablets containing ibuprofen. Well-recognized risk assessment tools – Fishbone diagram and Failure Mode Effects Analysis – were used to classify process parameters and then quantify the associated degree of risk. Since Dissolution test is influenced by numerous variables, these steps were fundamental in identifying the critical Dissolution test parameters.

The parameters below were initially thought to influence Dissolution Test the have been classified in five categories:

- Type/role of the excipients;
- Manufacturing process;
- Ibuprofen properties;
- Properties of excipients;
- The conditions under which the dissolution test is performed.

During medicine development, the formulation was designed in order to obtain a medicine with desirable active pharmaceutical ingredients release profile. Therefore, the ‘parameter type/role of the excipients used in the drug product’ will be disregarded from the FMEA.

Four categories were identified to constitute the Fishbone diagram, as it can be verified in Figure 8.

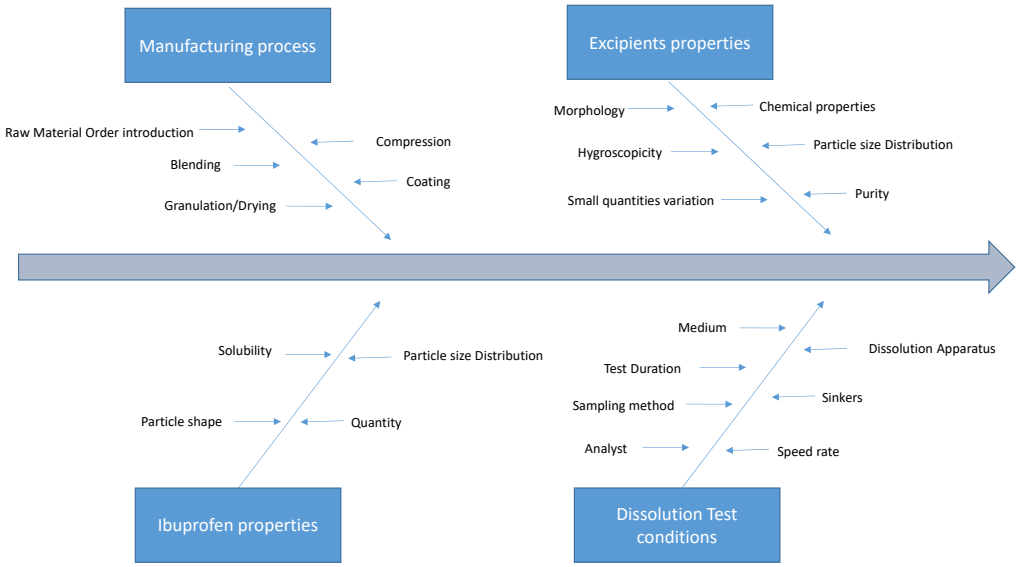


FIGURE 8. Fishbone diagram for Dissolution Test.

Having suspicious variables identified, FMEA was then applied to identify the critical parameters that impact Dissolution Testing. The latter will be used to compile data and follow the defined plan. FMEA was adopted as it is one of the Risk Assessment tools identified on Risk Assessment Guidelie, ICH Q9, and it is the one adopted by the holder of medicine in study.

Each parameter presented in the Fishbone diagram was ranked based on its Occurrence (O), its Impact (I), and its Detectability (D). A Risk Priority Number (RPN) was the calculated according to the scheme present in Table 1.

			(S) – SEVERITY			
			Minor - 1	Moderate - 2	Major - 4	Severe - 5
Probability	Almost certain/Unknown	5	5	10	20	25
	Likely	4	4	8	16	20
	Occasional	3	3	6	12	15
	Remote	2	2	4	8	10
	Extremely rare	1	1	2	4	5

			(C) - RISK CLASSIFICATION		
			Level 1	Level 2	Level 3
Detectability	Low	3	3	6	9
	Moderate	2	2	4	6
	High	1	1	2	3

TABLE 1. Risk priority Number determination: LOW - RPN (1-2) - A low priority RPN means that this function or component is not critical; MEDIUM - RPN (3-4) - A medium priority RPN means that this function or component is potentially critical; HIGH - RPN (6-9) - A high priority RPN means that this function or component is critical.

RPN values were used to separate critical parameters from the less critical ones for the present system. Parameters that are characterized by the highest RPN values were considered critical and therefore possibly strongly impacting Dissolution test.

2.2.1. Manufacturing Process

Manufacturing process is performed complying with Good Manufacturing Practice (GMP). GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product [24]. Being a GMP manufacturing process, this is a standard, properly validated and stablished process. Written procedures predict that no routine process starts until an adequate cleaning process is concluded (room, equipment, proper individual protection equipment for manufacturing operators, temperature, relative humidity and differential pressure confirmation). During batch release process, a double check is performed to all required measures to ensure batch conformity.

The manufacturing process of medicine under study involves the following steps:

- Weighing of materials;
- Intermediate Mixing (ibuprofen, Lactose monohydrate and corn starch);
- Binder preparation (purified Water + HPMC);
- Granulation/Drying;
- Intermediate Mixing (microcrystalline cellulose, croscarmellose sodium and colloidal anhydrous silica);
- Final mixture (magnesium Stearate);
- Compression;
- Coating (opadry and purified water);
- Packaging.

Reference is made to **Annex 3**.

The following steps/parameters related to the manufacturing process were identified as those which variability may have a stronger impact on Dissolution profile variances of immediate-release tablets containing ibuprofen: Raw material order introduction, Blending, Granulation/Drying, Compression and Coating steps.

2.2.1.1. Raw Material Order Introduction

Raw Material Order introduction was stablished according to each excipient role on final formulation and ibuprofen characteristics (poor flow and compaction), to obtain the tablet desired profile. Therefore, raw material order introduction is crucial (Severe impact).

Manufacturing process, including order material introduction, is properly validated and stablished. Manufacturing instruction of medicine describes the order in which raw materials are included during the process (Extremely rare probability).

Records from each batch describe what was done at each stage of the process. No process variation can be made without new process validation which implies dissolution compliance verification of final product on 3 batches (High detectability).

This factor has low risk so it can be excluded from risk assessment equation, as it can be verified on Table 2.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
RAW MATERIAL ORDER INTRODUCTION	Severe – 5	Extremely rare – 1	High - 1	Low – 2

TABLE 2. Raw Material Order Introduction Risk assessment.

2.2.1.2. Granulation

Wet granulation/Drying/Blend steps may impact medicine final dissolution profile, considering granule size obtained and water content (Severe impact) [25].

Manufacturing process, which includes granulation, drying and blend steps, was developed and properly validated using standard pharmaceutical guidelines. These steps were designed to obtain granules with specific sizes (sieving integrated) and with water content between 0.8 and 1.2%. This confirmation is obtained during drying and during blend steps. Therefore, it is unlikely to obtain granules without required characteristics (Remote probability and High detectability).

No variation can be made to manufacturing process without new process validation, which implies dissolution compliance verification of final product on 3 batches (High detectability).

This manufacturing step has Medium risk so it cannot be excluded from risk assessment equation, as it can be verified on Table 3.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
BLENDING/ GRANULATION/DRYING	Severe – 5	Remote – 2	High - 1	Medium – 3

TABLE 3. Blending/ Granulation/Drying steps Risk assessment.

2.2.1.3. Compression

Tablets with inadequate hardness will present unacceptable disintegration/dissolution profiles (Severe impact) [26].

The tablet porosity can be variable due to the batch-to-batch difference in compressibility of the powders/granules and variation of compressive stress in the high-speed tablet compaction. However, dissolution was never impacted due to this process (Remote probability).

While its impact is important, its presence is detectable by In Process Control strategy: hardness and disintegration time parameters. Manufacturing process, which includes compression instructions, is stablished, and properly validated. No variation can be made without new process validation which implies dissolution compliance verification of final product on 3 batches [27] (High detectability).

This manufacturing step has Medium risk so it cannot be excluded from risk assessment equation, as it can be verified on Table 4.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
COMPRESSION	Severe – 5	Remote - 2	High - 1	**MEDIUM – 3**

TABLE 4. Compression manufacturing step Risk assessment.

2.2.1.4. Coating

Tablet coating thickness could have high impact on the dissolution profile [28]. Coating solution is sparingly soluble in water and in most organic solvents. Coating process showed no stability constrains during medicine development process so interaction between excipients was disregarded. Coating represents 2% of the tablet (Major impact).

This step has several controls: weight build-up (nmt 2%); monitor and control of inside and outside temperature (which is important as ibuprofen has relatively low melting point, making it very susceptible to heat in the coating process); spray and pan rate definition; visual inspection for defects. Inhomogeneous and/or undercoated tablets can often easily be detected (Remote probability).

No variation can be made without new process, validation which, implies dissolution compliance verification of final product on 3 batches; However, disintegration time test takes place before this specific manufacturing step not allowing to consider coating thickness (Moderate detectability).

This manufacturing step has Medium risk so it cannot be excluded from risk assessment equation, as it can be verified on Table 5.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
COATING	Major – 4	Remote - 2	Moderate- 2	**MEDIUM – 4**

TABLE 5. Coating manufacturing step Risk assessment.

2.2.1.5. Excipients Properties

Since excipients quantities and their role, as previously discussed, were stablished during Medicine Development, being appropriate for medicine final role attributes of excipient, such as morphology, chemical properties, hygroscopicity, Particle size Distribution, Quantity, Purity, which have an important role on disintegration profile [29]. According to the ICH Q6 decision tree, the disintegration time is one of the limiting steps for a tablet dissolution. Disintegration time is very dependent of the arrangement of excipients on formulation [4] (Severe impact).

Formulation (type of excipients, quality profile and quantities) was stablished during Medicine Development. A small variation on the quantities of non-soluble excipients may impact final medicine release rate (Occasional probability).

All excipients are tested for quality parameters before integrating manufacturing process. It means that each relevant material property is confirmed. Additionally, the disintegration test is part of the in-process-control (IPC) strategy of the medicine (after compression). No variation can be made without a new process validation, which implies dissolution compliance verification of 3 batces of the final product (High detectability).

This parameter has Medium risk so it cannot be excluded from risk assessment equation, as it can be verified on Table 6.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
EXCIPIENTS PROPERTIES	Severe – 5	Occasional – 3	High - 1	**MEDIUM – 3**

TABLE 6. Excipients properties Risk assessment.

2.2.1.6. Ibuprofen Properties

2.2.1.6.1. Ibuprofen Assay

The active pharmaceutical ingredient concentration has an important impact on dissolution testing as stated by the Noyes–Whitney equation [16] (Severe impact).

Manufacturing instruction of medicine clearly describes the quantity of active pharmaceutical ingredient to include. However, being active pharmaceutical ingredient amount more than 70% of the tablet, any variance within specification could impact active pharmaceutical ingredient release profile (Occasional probability).

Records from each batch describe what was done at each stage of the process. Additionally, an inadequate amount of active pharmaceutical ingredient concentration will be detected during routine quality control assay testing. No variation can be made without a new process validation which implies dissolution compliance verification of 3 batches of the final product [27] (High detectability).

This parameter has Medium risk so it cannot be excluded from risk assessment equation, as it can be verified on Table 7.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
IBUPROFEN ASSAY	Severe – 5	Occasional – 3	High - 1	**MEDIUM – 3**

TABLE 7. Ibuprofen Assay Risk assessment.

2.2.1.6.2. Ibuprofen Particle size distribution

Tablet dissolution can be influenced by the physical properties of the active pharmaceutical ingredient. According to the Noyes–Whitney equation, the surface area has an important impact on dissolution testing [16] (Severe impact).

Small variances within specification of the particle size distribution (PSD) test could impact drug release profile (Occasional probability).

No variation regarding active pharmaceutical ingredient source can be made without new process validation execution, which implies a dissolution compliance verification of 3 batches of the final product [27] (High detectability).

This parameter has Medium risk so it cannot be excluded from risk assessment equation, as it can be verified on Table 8.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
PARTICLE SIZE DISTRIBUTION	Severe – 5	Occasional – 3	High - 1	**MEDIUM – 3**

TABLE 8. Particle size distribution Risk assessment.

2.2.1.7. Ibuprofen Solubility

From a regulatory point of view, only BCS class I and III compounds allow for surrogate testing in the form of disintegration as defined by the ICH Q6 decision tree. The main rationale for limiting reducing tests to highly soluble compounds is related to the fact that tablet dissolution of these medicines is largely independent of the rate ofactive pharmaceutical ingredient solubilization being the overall dissolution profile dictated by tablet disintegration. Ibuprofen belongs to Class II. However, the active pharmaceutical ingredient is highly soluble at the pH the Dissolution Test is performed, pH 7.2 (minor severity and extremely rare probability).

No variation regarding active substance source can be made without new process validation execution, which implies a dissolution compliance verification of 3 batches of final product [27] (high detectability).

This parameter has Low risk so it can be excluded from risk assessment equation, as it can be verified on Table 9.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
SOLUBILITY	Minor – 1	Extremelly rare – 1	High - 1	**LOW – 1**

TABLE 9. Ibuprofen Solubility Risk assessment.

2.2.1.8. Ibuprofen Particle Shape

Tablet dissolution can be influenced by the physical properties of active pharmaceutical ingredient (morphology, density, flow properties and tabletability). Specifically for ibuprofen, studies have shown that although ibuprofen may adopt various particle morphologies, due to differences in synthesis process, it does not appear to exhibit genuine polymorphism. Accordingly, the crystallization conditions did not alter the polymorphic nature of ibuprofen, and hence no marked difference in dissolution behaviour was observed [30] (Moderate impact).

For both approved suppliers of ibuprofen, optical rotation specification and bulk density (tapped and untapped) have some specification range with overlapping results.

Batches from both sources are 0.00° for optical rotation. Therefore, particle shape of both is considered equivalent. (Extremely rare probability and High detectability).

No variation regarding active pharmaceutical ingredient source can be made without new process validation execution, which implies a dissolution compliance verification of final product on 3 batches (high detectability).

This parameter has Low risk so it can be excluded from risk assessment equation, as it can be verified on Table 10.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
PARTICLE SHAPE	Moderate - 3	Extremelly rare – 1	High - 1	**LOW – 1**

TABLE 10. Particle shape Risk assessment.

2.2.2. Dissolution Test Conditions

Both sampling and dissolution test procedures are determinant for dissolution profile consistency (major impact).

Dissolution Test conditions are stablished in a very strict way (according to European Pharmacopoeia, monograph 2.9.3.). Sampling process is qualified, and it follows a strict procedure. Records of each step are also strictly performed according GMP and GLP rules (Extremely rare probability and High detectability).

Additionally, no variation can be made without new process validation and change impact evaluation (High detectability).

This parameter has Low risk so it can be excluded from risk assessment equation, as it can be verified on Table 11.

PARAMETER	RISK CALCULATION			
	SEVERITY	PROBABILITY	DETECTABILITY	RPN
DISSOLUTION TEST CONDITIONS	Major – 4	Extremely rare – 1	High – 1	**LOW**

TABLE 11. Experimental conditions and testing Risk assessment.

2.3. CRITICAL QUALITY ATTRIBUTES DATA COMPILATION

The goal of designing a tablet formulation and its manufacturing process is to release and deliver orally the correct amount of the active pharmaceutical substance in the right form, at or over the accurate time period, in the desired physiological location and to have its chemical integrity protected to that point. I.e., besides the importance of physical and chemical properties of the active pharmaceutical substance being formulated into a tablet, the actual physical properties, manufacturing process, and complete chemical properties of the core tablet can have a profound effect on the efficacy of the medicine being administered. Thus, evaluation of tablet properties is an important aspect of quality control ensuring production of tablets with prompt bioavailability [26].

The FMEA risk assessment approach identified the following parameters as having the major impact on Dissolution profile of the medicine under study:

- Granulation manufacturing step (medium);
- Compression manufacturing step (medium);
- Coating manufacturing step (high);
- Excipients properties (medium);
- Active pharmaceutical ingredient particle size distribution (medium);
- Ibuprofen assay (medium).

For the manufacturing steps identified by having impact on the Dissolution profile of medicine under study, parameters that best characterize their quality shall be identified. For Granulation manufacturing step, water quantity would provide more information than other parameter regarding this step [31]; for Compression manufacturing step, hardness is the core physical properties that best characterize this step; Finally, for Coating manufacturing step, weight build-up test confirms this step conclusion.

Active pharmaceutical ingredient particle size distribution, granules water content, tablet hardness, coating thickness, disintegration time, and ibuprofen assay are the identified parameters that may extensively affect the dissolution profile of the medicine under investigation. In the next chapters, before performing data analysis, it will be briefly characterized how these parameters may impact active pharmaceutical ingredient release profile.

2.3.1. Hardness

Hardness is a measure of tablet strength as it gives insights into the force required to break a tablet. Generally, hardness is dependent on the type and concentration of binder, tablet height to diameter ratio and compression force [26].

During tablet manufacturing, especially during compression step, pharmaceutical powders are subjected to compressional forces to make a solid stable compact called tablet. These powders vary in their mechanical behaviour during compression: some deform elastically, plastically or they fragment. The elastic deformation is reversible, the plastic deformation is irreversible, while in fragmentation, particles break-up into a number of smaller, discrete parts. Deformation mechanism of materials is affected by properties of that material and compression force and speed [33]. As the compression force increases, the powder becomes densely packed with less inter-particulate void spaces for relative particle movement. At this stage, stress starts to build-up at the particle contact point in the die and the material begins to deform. Once the particles have deformed above the elastic limit of the material, even after the removal of the compression force, it becomes irreversible. But if the force is not strong enough to exceed the elastic limit of the particle, an unstable tablet that crumbles is formed. In tablet compression, materials have a dependant compression force limit, and materials under a compression goes below this value, do not form a coherent compact, while when it goes above the limit, the materials form a coherent tablet with increasing strength proportional to the compression force applied. If the compression force is too high, it may not lead to an appreciable increase in hardness but could adversely affect the dissolution of the tablet and may also cause internal stress cracks, leading to tableting defects [33]. This phenomenon can be explained by the fact that dissolution is dependent on disintegration, which is mostly influenced by tablet hardness.

Ibuprofen 600 mg is tested for hardness after compressing manufacturing step. The crushing strength is determined by diametric compression of each of ten tablets per sample using a motorized hardness tester (Campbell Electronics, Model HT-30/50, India). The mean ± SD is calculated. The limit for this test is 70 – 130 N.

2.3.2. Active pharmaceutical ingredient particle size distribution

As stated on Noyes–Whitney equation, the particle size distribution has a very important role on dissolution testing. Particle technology in pharmaceutics is a technique to modify physicochemical, micrometrics and biopharmaceutical properties of the poorly soluble active pharmaceutical ingredient, thereby improving their solubility [34]. Among various techniques for solubility enhancement, physical modifications of medicines such as reducing the particle size are common approaches to increase active pharmaceutical ingredient solubility. Apart from conventional micronizing techniques, particle technology now deals with various particle and nanoparticle engineering processes as promising methods of improving active pharmaceutical ingredient solubility [34].

Ibuprofen particle size distribution is measured in routine by laser diffraction spectroscopy. Approved specification is 60.0 – 130.0 microns.

2.3.3. Granules water content

Water content was also an identified parameter which risk was considered significative enough to be include on the study. Water may interact with pharmaceutical solids at all stages of the manufacture process, ranging from the synthesis of raw materials to the storage of the final dosage form. The interactions of water with powders can be, therefore, a major factor in the formulation, processing and product performance of solid pharmaceutical dosage forms [35]. Excessive or deficient moisture content can adversely impact the physical properties of a pharmaceutical product, which in turn affect the chemical reactivity and binding properties that define the product's shelf-life.

Having very high levels of water may cause agglomeration of powder particles that constitute the formulation and may result in a poor crumbly tablet; on other hand, having less moisture than needed may cause the tablet to fall apart. Powder of excipients may not flow if there is high moisture and for active pharmaceutical ingredients, they can crystallize or even change their form [36].

Therefore, controlling moisture content is part of the very careful process control required during manufacture.

Even though, storage humidity may have a significant effect on physical and chemical properties of excipients and active pharmaceutical ingredients, for the medicine under study, the development studies which includes stability data showed compatibility, i.e., no significant loss of potency, increase in moisture and increase in related substances were verified. Additionally, during all last 10 years of experience on manufacturing Ibuprofen medicine and studying its stability, no impact on dissolution profile was recorded.

The test performed during manufacturing process to control Granulation step regards Loss on Drying under the following conditions: Halogen balance, 2.0-3.0 g, 105°C, 10 min. Granulation, drying and blend steps are designed to obtain granules with water content between 0.8 and 1.2%. This confirmation is obtained during drying and during blend steps.

2.3.4. Coating thickness

Coating is an important step of the manufacturing process that is often used for functional and aesthetic reasons. Coating strategy is the most widely used approach to solve several constraints found during manufacturing, transport, storage, and clinical use of drug products. For example, tablets containing active pharmaceutical ingredients that are sensitive to light, oxidation, or moisture can be protected by film coating, leading to increased stability of final

medicine during manufacturing and storage [37].

In the case of the medicine under study, coating has no functional purpose as it only applied to reduce nucleus rugosity and allow a homogeneous aspect to the tablet. Coating solution used is sparingly soluble in water and in most organic solvents.

It is a challenging operation in terms of achieving the desired amount of coating thickness and coating uniformity. To ensure the quality of coated dosage forms it is desirable to have an in-process control strategy during this manufacturing step to monitor the coating operation and detect the end point of the process [38]. The tablets are coated using auto coater machine until about 2% weight gain is achieved.

2.3.5. Desintegration time

An immediate-release dosage form should be designed to disintegrate in such a way to efficiently liberate its active ingredient(s) and make it available for absorption. By choosing suitable chemical and physical properties, tablets can be formulated in order to immediately release their active pharmaceutical ingredients following oral administration (immediate-release tablets) or, in alternative, be formulated to modify the active pharmaceutical ingredients release profile aiming to achieve improved therapeutic efficacy, reduced toxicity, and improved patient compliance and convenience (the called modified-release tablets). Immediate-release tablets are designed to fully disintegrate and dissolve upon exposure to physiological fluids within a short period of time [18].

After the liquid wets the tablet surface and penetrates the pores, disintegration takes place in two steps: first, tablet disintegration into small granules, and second, disaggregation or granule disintegration. The first step is important for the rate of initial active pharmaceutical ingredients release from the tablet. If no disintegration would occur, only the API near the surface of the compact would dissolve.

The disintegration test basically consists of placing a medicine in an immersion medium under defined experimental conditions and measuring the time taken for its to disintegrate [39, 40].

The methodology used to evaluate the Disintegration profile of the medicine under study in routine is the one defined on test monograph of Ph. Eur. (**Annex 2**). This test predicts to use water as the immersion fluid maintained at 37 ± 2º C. Tablets are observed for 60 minutes. The test is met if all of 6 dosage units in the six tubes of the bask have disintegrated completely. The Disintegration Test monograph defines complete disintegration as the *"state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core"*. The value recorded is the minimum disintegration time recorded, which specification is not more than 10 minutes.

2.4. BATCHES DATA VARIABILITY ASSESSMENT

Before proceeding to the data analysis to identify and assess the existence, or not, of a mathematical relationship between the dissolution parameter and the variables identified in the context of risk analysis, it is necessary to confirm that the available data for the years 2018 and 2019 have enough variability.

This approach is acceptable for scientific studies such as those needed to perform to support a Quality By Design as can be consulted on Q8, Q9, & Q10 Questions and Answers *"In developing design spaces for existing products, multivariate models can be used for retrospective evaluation of historical production data. The level of variability present in the historical data will influence the ability to develop a design space, and additional studies might be appropriate."*

Medicine under study has been manufactured at industrial scale for more than 10 years.

Documentary records of 58 batches produced for the last 2 years of production, from 2018 to 2019 year, in the same manufacturing site are being considered: the equipment and facilities used are the same. During the mentioned period, no significant change controls were registered for the established manufacturing process. Reference is made to Annex -1 for this data.

In order to confirm that these 58 batches data show sufficient variability a whisker plot tool was used. Whisker plot length gives an indication of the sample variability and the line across the box shows where the sample is centered.

Whisker plot shows the variability in the inputs and allows to compare with the variability in the dissolution parameters (output). I.e., it shows how data are distributed and illustrate the variability of a data set.

As the variables have different units, comparison is difficult. As so, to overcome this constraint, it was performed an adaptation for each variable, by applying the parameter RANGE/AVERAGE (RANGE = MAX-MIN), then a dimensionless number capable of being compared is achieved per each parameter.

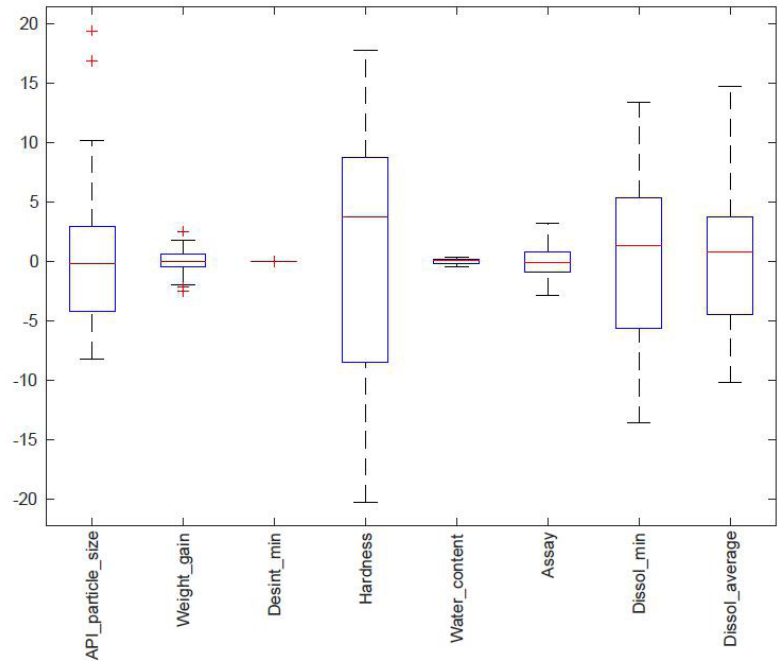


FIGURE 9. Boxplot of batches data.

In the above plot on Figure 9, the active pharmaceutical ingredient particle size, weight gain, disintegration time, water content, assay and hardness populations appear to have similar centers and are reasonably symmetric, which exceed those of dissolution.

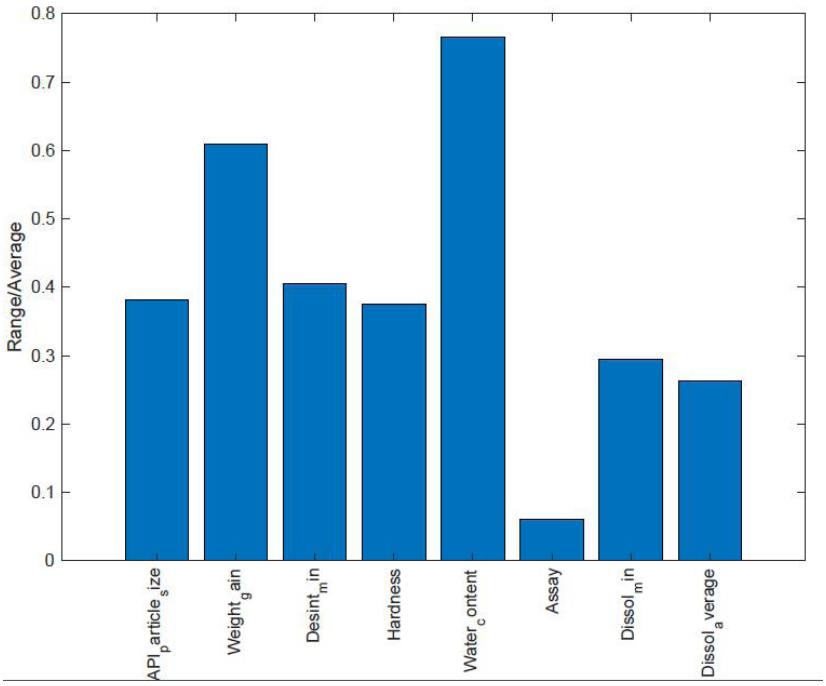


FIGURE 10. Boxplots to compare variables at once.

The Figure 10 shows that a greater variation in the 6 parameters (excluding the active pharmaceutical ingredient assay) has more variability than that obtained for the dissolution parameters, which reinforces the robustness of the system.

Specifically, for the active pharmaceutical ingredient quantity, the variability of values between batches was found to be limited. This finding is justified by the narrow specification regarding the dosage of the the active pharmaceutical ingredient. The batch assay, in routine, must comply with range 90-110%. No batch is placed on the market with a lower or higher amount of the active pharmaceutical ingrediente. Being this an absolutely limiting principle for the commercialization of batches, it is not relevant to consider another or a wider range of values in the study.

It can be concluded that available data has sufficient variability enabling, this way, o be used in the next step, which is the evaluation of eventual relation between Critical Quality Attributes and Dissolution analysis.

2.5. RELATION BETWEEN CRITICAL QUALITY ATTRIBUTES AND DISSOLUTION ANALYSIS

To evaluate 4th requirement of ICH Q6A guideline *"Has a relationship been determined between disintegration and dissolution?"* it was adopted Multivariate Data Analysis Software (SIMCA) version 14 to estimate the Partial Least Squares (PLS) model with following quantitative variables: active pharmaceutical ingredient particle size, weight gain, disintegration min hardness, water content and active pharmaceutical ingredient assay.

SIMCA is a software developed by Umetrics, which is mainly used for the methods of principle component analysis (PCA) and partial least square (PLS) regression. The multivariate-regression methods most frequently used to study relation between variables are PLS regression. The main goal of PLS is to establish a linear link between two matrices, the spectral data X and the reference values Y. This technique consists of modelling both X and Y in order to find out which variables in X matrix will best describe Y matrix.

SIMCA/PLS strategy is typically used to identify local models for defined data groups and to predict a probable class membership for new observations. It models complex systems and allows gaining a deep understating of the processes [40].

This section intends to study, not only the relation between disintegration and dissolution, but also the eventual relationship between dissolution and other variables.

Fours models were studied:

- Model with data from 58 batches: relation between average percentage of Dissolution (%) and active pharmaceutical ingredient particle size (microns), weight gain (mg), minimum disintegration time (minutes and seconds), water content (%) and active pharmaceutical ingredient quantity (%);
- Model with data from 32 batches (year 2018): relation between average percentage of Dissolution (%) and active pharmaceutical ingredient particle size (microns), weight gain (mg), minimum disintegration time (minutes and seconds), water content (%) and active pharmaceutical ingredient quantity (%);
- Model with data from 24 batches (year 2019): relation between average percentage of Dissolution (%) and active pharmaceutical ingredient particle size (microns), weight gain (mg), minimum disintegration time (minutes and seconds), water content (%) and active pharmaceutical ingredient quantity (%);
- Model with data from 58 batches: relation between average percentage of Dissolution (%) and disintegration time (minutes and seconds).

SIMCA (58 batches; Y: Dissolution average; X: API particle size, Weight gain, Disintegration min Hardness, Water content, Assay)

For each model component in a PLS model, SIMCA displays two bars: the green (R2) and the blue (Q2) bar, according to Figure 12.

R2 represents the percent of variation of the data explained by the model. R2 is a measure of fit, i.e. how well the model fits the data. Obtained model presents a poor R2 (0.268), as it can be seen in Figure 12, which may mean poor reproducibility (much noise) or that variables do not explain Dissolution profile. A large R2 (close to 1) is a necessary condition for a good model, but it is not sufficient. Models with large R2 can be poor if they cannot predict (low Q2).

Q2 is the percent of variation of the data predicted by the model according to cross validation. Q2 indicates how well the model predicts new data. A large Q2 (Q2 > 0.5) indicates good predictivity. Obtained model presents a poor Q2 (0.214), as it can be seen in Figure 11 and 12, which may mean data have much noise, the relationship between variables and dissolution is poor or the model has outliers.

TYPE	A	N	R2X (cum)	R2Y (cum)	Q2 (cum)
PLS	1	58	0,274	0,268	0,214

FIGURE 11. Characterization of model.

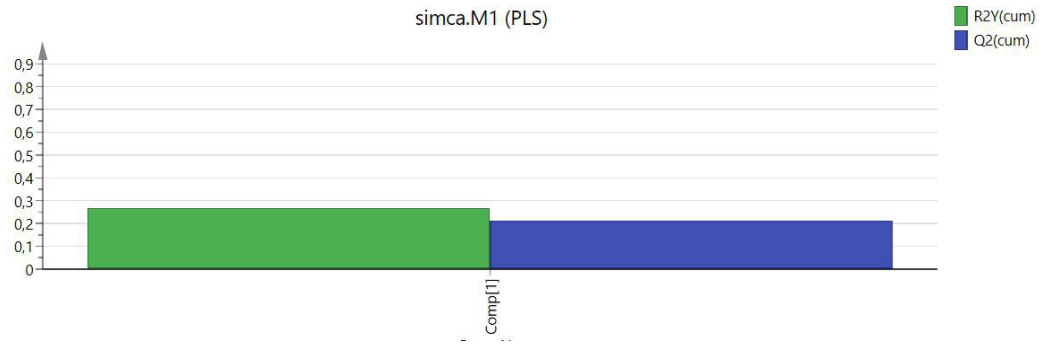


FIGURE 12. SIMCA Plot representing R2 and Q2 of model.

The VIP (Variable Importance for the Projection) plot, represented on Figure 13, summarizes the importance of the active pharmaceutical ingredient particle size, weight gain, disintegration time, hardness, water content and assay variables to correlate them with respective Dissolution results.

VIP-values larger than 1 indicate “important” X-variables, and values lower than 0.5 indicate “unimportant” X-variables. The interval between 1 and 0.5 is a gray area, where the importance level depends on the size of the data set.

According to Figure 13, weight gain and disintegration time are considered important variables, i.e., contribute more to explain Dissolution results.

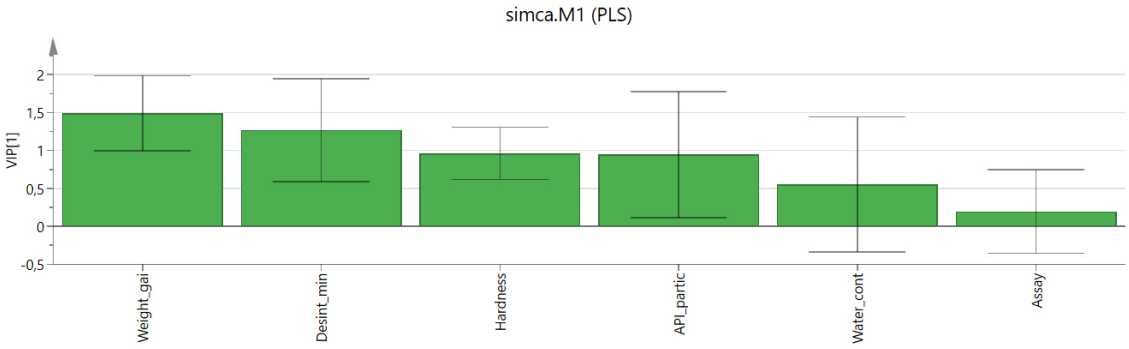


FIGURE 13. SIMCA VIP Plot presenting variables per importance.

For a PLS model, SIMCA also displays the coefficient plot represented in Figure 14. The coefficients refer to the PLS model being rewritten as a regression model. By default, regression coefficients related to scaled and centered X-variables are displayed. This scaling of data makes the coefficients comparable. The size of the coefficient represents the change in Dissolution variable when the variables vary from 0 to 1, while the other variables are kept at their averages. Thus, these coefficients express how strongly Dissolution Test is correlated to the systematic part of each of the variables. The error bars indicate the confidence intervals of the coefficients. The coefficient is significant (above the noise) when the confidence interval does not include zero.

According to Figure 14, weight gain contributes positively to Dissolution results, i.e., when weight gain increases the Dissolution percentage also increases; Regarding Disintegration Time, an inverse relation is obtained, as when Disintegration Time decreases, Dissolution percentage increases. Remaining variables do not show to be important for Dissolution profile.

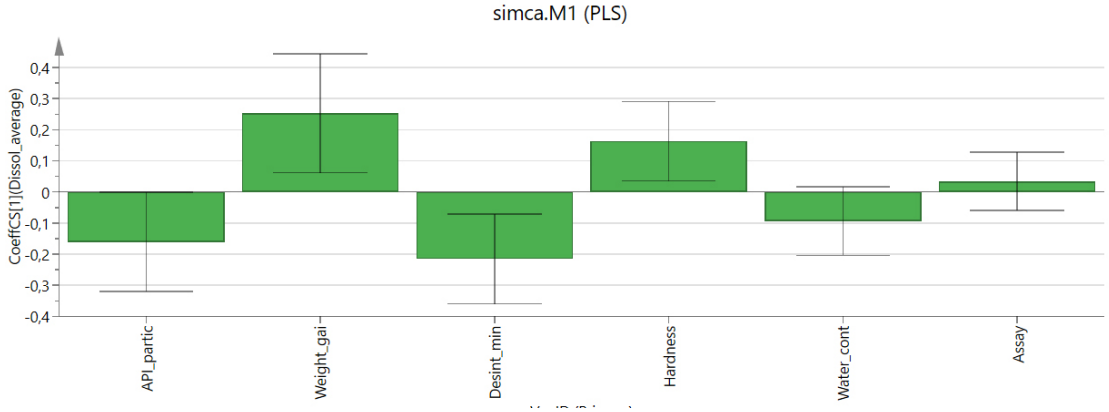


FIGURE 14. SIMCA Coefficient Plot presenting variables per importance.

Plot presented in Figure 15 displays the observed versus predicted values, of Dissolution (Y) and variables (X). With a good model all the points would fall close to a 45 degree line. As already shared, the R2 parameter of the regression line indicates the goodness of fit. With less good models the points are scattered around the regression line as it can be seen in our model. Our model has an inclination; however, it is scattered.

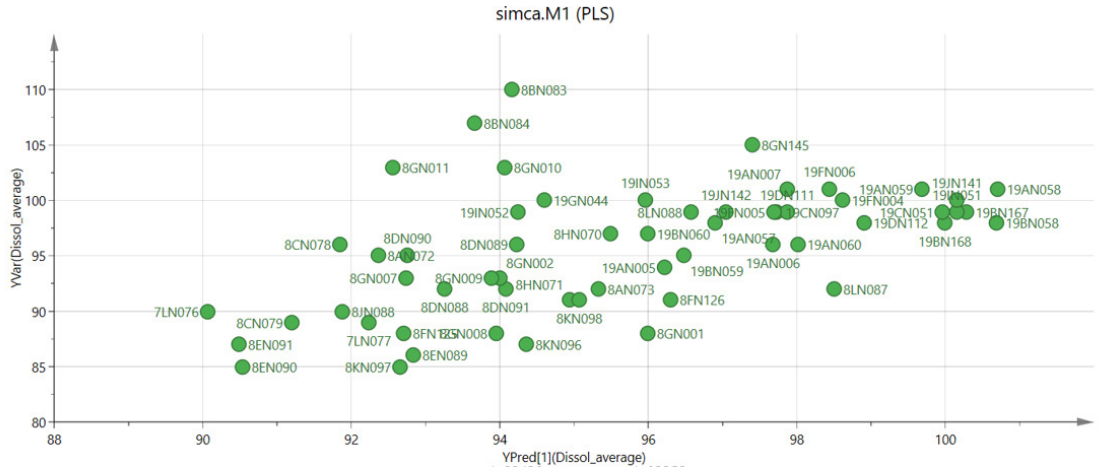


FIGURE 15. SIMCA observes versus predicted.

The scores on Figure 16 are new variables summarizing the X-variables. The score plot is a map of the observations: the scores are orthogonal, i.e., completely independent of each other. There are as many score vectors as there are components in the model.

The adopted score, t1 first component, explains the largest variation of the X space, followed by t2 etc. In this model, t1 has the best R2 and Q2 (0,268 and 0,214, respectively) compared to t2 (0,295 and 0,179, respectively).

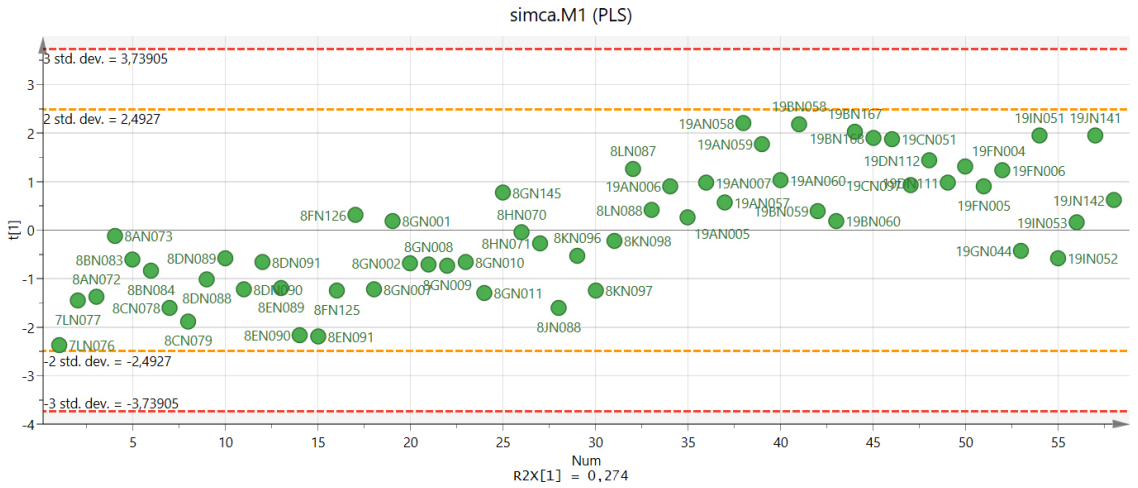


FIGURE 16. Model with 1 component distribution.

DmodX, as stated on Figure 17, is the distance of a batch to the model. By default, DModX is displayed in normalized unit, that is the absolute DModX divided by the pooled residual standard deviation of the model.

The critical value of DModX (Dcrit), is computed from the F-distribution.

Observations with a DModX twice as large as Dcrit are moderate outliers. This indicates that these observations are different from the normal observations with respect to the correlation structure of the variables.

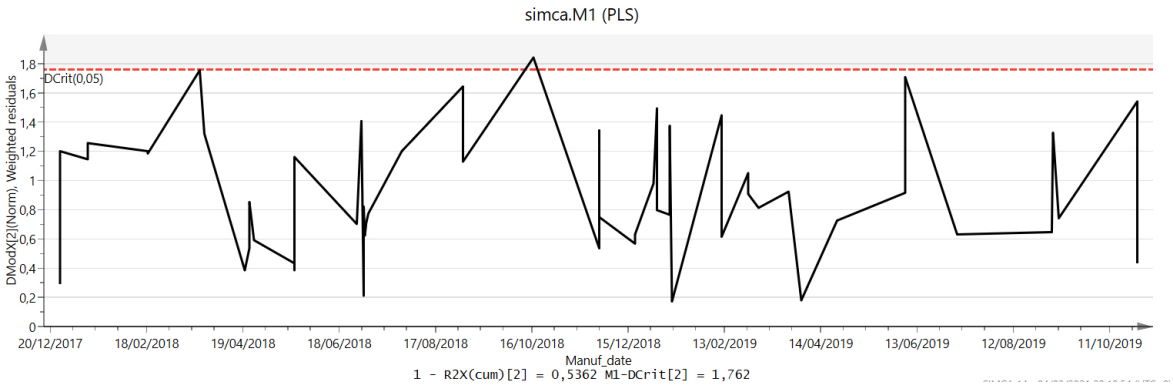


FIGURE 17. DmodX.

Data obtained for first year was segregated from the data recorded during the second year and both were evaluated on SIMCA, separately, in order to evaluate if small differences in data profile between both years could justify obtaining a model with low R2 and low Q2.

SIMCA (32 batches 2018; Y: Dissolution average; X: API_particle_size, Weight_gain, Desint_min Hardness, Water_content, Assay)

MODEL	TYPE	A	N	R2X (cum)	R2Y (cum)	Q2 (cum)
M1	PLS	1	32	0,185	0,227	-0,00565

FIGURE 18. Characterization of model.

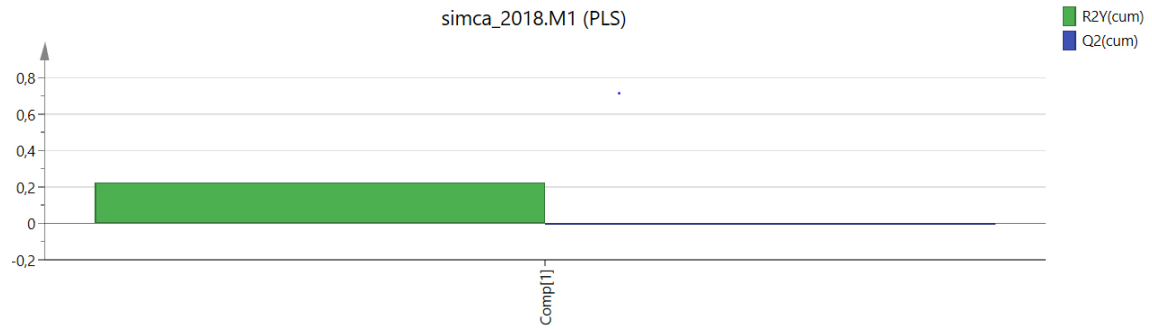


FIGURE 19. SIMCA Plot representing R2 and Q2 of model.

SIMCA (24 batches 2019; Y: Dissolution average; X: API_particle_size, Weight_gain, Desint_min Hardness, Water_content, Assay)

TYPE	A	N	R2X (cum)	R2Y (cum)	Q2 (cum)
PLS	1	24	0,43	0,191	0,009

TABLE 12. Characterization of model.

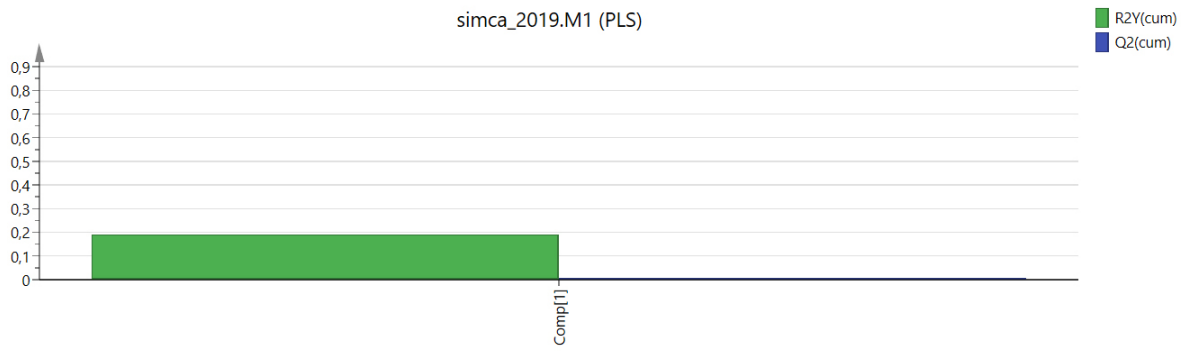


FIGURE 20. SIMCA Plot representing R2 and Q2 of model.

R2 and Q2 values of both models, either from year 2018 and from year 2019, showed models with less quality.

It was performed a last model that relates Dissolution Test (Y) with Disintegration Time (X) only, considering data from both years.

SIMCA (58 batches; Y: Dissolution average; X: Disintegration)

TYPE	A	N	R2X (cum)	R2Y (cum)	Q2 (cum)
PLS	1	58	1	0,112	0,101

FIGURE 21. Characterization of model.

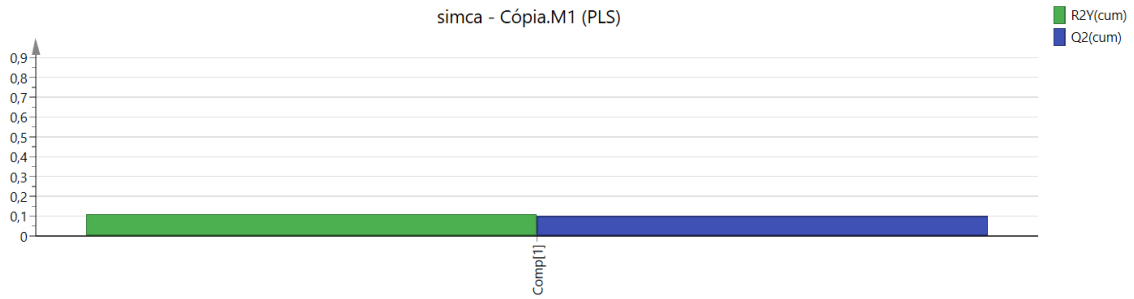


FIGURE 22. Fishbone diagram for Dissolution Test.

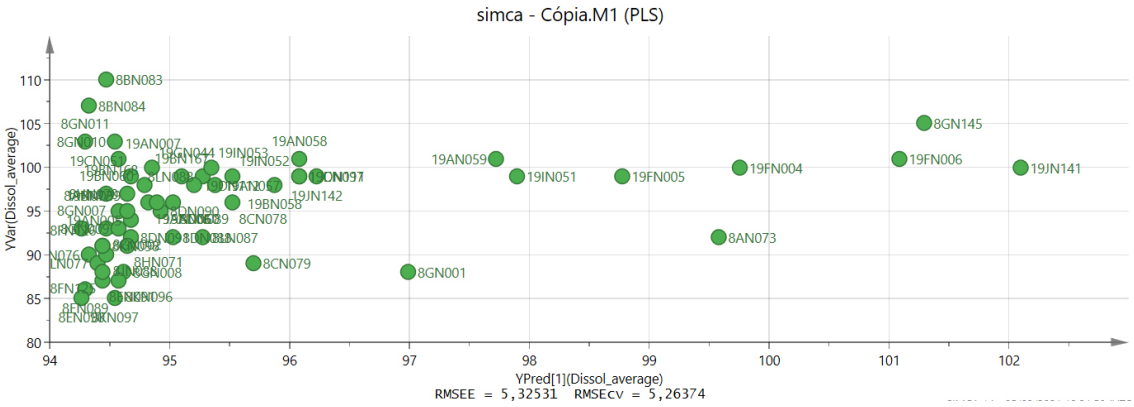


FIGURE 23. SIMCA observes versus predicted.

A relation between parameters Dissolution average and Disintegration Time can be stablished (R2=0.112; Q2=0101). These values show that obtained model has lack of reproducitibility capacity and low predictability capacity.

3.

RESULTS AND DISCUSSION

3. RESULTS AND DISCUSSION

According to the ICH Q6A Decision Tree 7 (Figure 2), a disintegration test can be used as a surrogate for a dissolution test if the following conditions are met:

1. The dosage form does not exhibit modified release characteristics;
2. The drug has a dose/solubility ratio not less than 250 mL over a pH range of 1.2–6.8;
3. More than 80% of the dose is dissolved within 15 minutes at pH values of 1.2, 4.0, and 6.8;
4. A relation has been determined between dissolution and disintegration.

These 4 requirements will be discussed, one by one, on this Results and Discussion Chapter, as a summary and an integrated analysis of what has been established and analysed.

1. The dosage form does not exhibit modified release characteristics.

Dosage form of medicine under study consists of an immediate release form.

Therefore, first requirement is filled.

2. The drug has a dose/solubility ratio not less than 250 mL over a pH range of 1.2 – 6.8.

Second requirement intends to ensure that active pharmaceutical ingredient is soluble all over the gastrointestinal tract. This requirement is set by default to ensure unequivocal solubility properties of the active pharmaceutical ingredient. However, for those substances which absorption target is a specific GI tract area with a specific pH range, the criteria is considered conservative. Such is the case of ibuprofen on formulation under study, which target site of active pharmaceutical ingredient absorption is the jejunal section of the small intestine, where pH values are between 7 and 9. For this reason, monograph defined for Ibuprofen Tablets Dissolution Test to be performed only at pH 7.2. Ibuprofen is highly soluble at pH 7.2, fitting, this way, the criteria for a biowaiver.

Accordingly, ibuprofen may also fit in the newly proposed ‘‘intermediate solubility class’’ suggested for acids and bases that are highly soluble at either physiologically relevant pH. Current publications also suggest pH-dependent soluble, highly permeable, weak acidic

ionizable active pharmaceutical ingredient compounds should be handled like BCS class I drugs [19].

3. More than 80% of the dose is dissolved within 15 min at pH values of 1.2, 4.0, and 6.8.

Formulation under study fills this requirement at pH 7.2, which is the pH of the medicine GI tract target and the pH at which Dissolution Test described on product monograph is performed, against a criterion of 60 minutes. Reference is made to requirement number 2.

4. A relation has been determined between dissolution and disintegration.

Risk analysis is an important step in defining best control strategy application. In the first part of the study, risk analysis was performed, and six parameters were identified as potential impact factors: active pharmaceutical ingredient particle size; coating weight gain; hardness; water content; active pharmaceutical ingredient assay and disintegration time.

As Dissolution test results after 60 minutes were similar within all batches (100% of active pharmaceutical ingredient dissolved), it was not possible to evaluate, at this time point, dissolution profile of the medicine. Therefore, specification of Dissolution test was adapted in order to measure active pharmaceutical ingredient dissolved percentage at 20 min with some specification, allowing us to better understand release product behaviour.

Regarding study performed with data to evaluate relation between Dissolution Tests and relevant parameters, obtained models showed low quality probably due to below facts:

- Medicine under study is composed by almost 80% of active pharmaceutical ingredient ibuprofen, being excipients expression much lesser; ibuprofen is pH dependent, is highly soluble at pH 7.2, the Dissolution test condition. Once exposed to dissolution test environment, it was verified that tablets start disintegrating and dissolving at the same time;
- Considering differences between Dissolution test and Disintegration test conditions, it would be challenging to obtain good mathematical correlation between the both;
- Disintegration time value regards the minimum obtained; Dissolution Test value is an average percentage.

These facts can explain why water content and hardness showed to be “unimportant” variables. Small variances on formulation characteristics such as tablet hardness and water content is unlikely to impact final medicine dissolution profile of a medicine with referred characteristics, not being able this way to obtain a mathematical relation either between these variables and dissolution and also between disintegration and dissolution.

According to plots of Figures 13 and 14, only weight gain and Dissolution Time parameters were found to statistically affect dissolution results of the tablets, under the ranges studied.

Active pharmaceutical ingredient particle size and its quantity showed to be statistically "not relevant" variables. It can be explained by the fact ibuprofen is highly soluble and therefore, its intrinsic solubility is not affected by small differences on its particle size or on its quantity as expected for such components [39].

This allows to conclude that formulation is robust in terms of dissolution.

According to the 2017 guideline *"Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action"* this conclusion is expected for the very highly soluble active pharmaceutical ingredient, of BCS class I and III: *"'It may not always be possible to detect any differences in dissolution behaviour after meaningful changes have been made in material specifications and/or manufacturing parameters. In these cases, the method may be considered to be adequate without further justification or be replaced by a disintegration test".*

Considering the above and the fact, even being a poor relation due to robustness of formulation in terms of Dissolution, a relation between Dissolution and Disintegration Test has been stablished. It means that Disintegration test, already performed during manufacturing process in routine, may be sufficient to replace dissolution testing as a routine test for medicine under study.

All presented data support the replacement of dissolution by disintegration testing according to ICH Q6A.

4.
CONCLUSION

4. CONCLUSION

Legislation applied to the pharmaceutical industry world has become increasingly demanding over the years, with the aim of protecting the interest of patients, specifically, with the ultimate goal of providing these, medicines with the desired quality, safety and effective profile.

While it becomes more complex, it also includes opportunities to balance requirements. These flexibilization opportunities are intended to drive companies on the path of using their financial, human and scientific resources on the route of innovation, development and continuous improvement.

When considering eliminating a quality parameter from the set of parameters that are used to conclude about the final quality of a batch, such as Dissolution Test, it is essential to have confidence in the active pharmaceutical ingredient solubility behaviour and on manufacturing process robustness, and to evidence that the remaining set of tests, performed during manufacturing process, provides the necessary information to guarantee visibility of active pharmaceutical ingredient release profile in the formulation.

Risk analysis, identification of critical formulation/process variables, understanding the effects of these critical variables and interactions on key product quality attributes are essential steps to achieve process awareness and offer opportunities to develop control strategies while ensuring final product quality. This approach is in line with the concept of Real Time Release.

From the data generated during 10 years of experience manufacturing medicine under study, a sample was selected of the last 2 years. This selection considered the fact due that data was generated at the same manufacturing site, with the same manufacturing and analysis equipment. However, the remaining manufacturing data also supports the robustness of the process (absence of results out of specification and out of trend limit): all batches complied with product monograph dissolution criterion (80% dissolved in 60 minutes) at 20 minutes.

The 2018 and 2019 data, the parameters identified in the risk analysis processes, were considered sufficient to assess and conclude about the relationship between disintegration and dissolution and, consequently, the robustness of the process to obtain a formulation with a predictable dissolution profile.

Considering this fact, a poor mathematical relation was established between disintegration and dissolution parameters.

Having remaining ICH Q6A requirements discussed, it can be concluded that, for medicine bein studied and the current approved manufacturing parameters, if disintegration complies

with specification, the routine test and specification predicted on the product monograph for Dissolution will consistently comply with specifications (to dissolve 80% of active pharmaceutical ingredient in 60 minutes).

Disintegration is an important quality control test today. With a proper understanding and demonstration or justification of the mechanistic details of active pharmaceutical ingredient dissolution from the formulation, dissolution testing might be replaced by disintegration testing for certain medicines as a performance test. Disintegration testing can save time and cost for Quality Control departments in the pharmaceutical industry due to its simplicity.

Therefore, it is proposed to eliminate the Dissolution Test from the finished product specification. It is also proposed that the dissolution test is used whenever there is a suspicion on the final quality of the batch.

5.

ANNEXES

ANNEX 1

Ibuprofen Tablets USP Monograph

U.S. PHARMACOPEIA

Search USP29 Go

Ibuprofen Tablets

» Ibuprofen Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{13}H_{18}O_2$.

Packaging and storage— Preserve in well-closed containers.

Labeling— Where the Tablets are gelatin-coated, the label so states.

USP Reference standards ⟨ 11 ⟩ **—** *USP Ibuprofen RS*.

Identification—

A: Grind 1 Tablet to a fine powder in a mortar, add about 5 mL of chloroform, and swirl. Filter the mixture, and evaporate the filtrate with the aid of a stream of nitrogen to dryness: the IR absorption spectrum of a mineral oil dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of *USP Ibuprofen RS*.

B: Its retention time, relative to that of the internal standard, determined as directed in the *Assay*, corresponds to that of *USP Ibuprofen RS*.

Dissolution ⟨ 711 ⟩ **—**

Medium: pH 7.2 phosphate buffer (see under *Buffers* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Procedure— Determine the amount of $C_{13}H_{18}O_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 221 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of *USP Ibuprofen RS* in the same medium. [NOTE—Where the Tablets are labeled as gelatin-coated, determine the amount of $C_{13}H_{18}O_2$ dissolved from the UV absorbance at the wavelength of maximum absorbance at about 266 nm from which is subtracted the absorbance at 280 nm, in comparison with the Standard solution similarly measured.]

Tolerances— Not less than 80% *(Q)* of the labeled amount of $C_{13}H_{18}O_2$ is dissolved in 60 minutes.

Uniformity of dosage units ⟨ 905 ⟩ : meet the requirements.

Water, *Method I* ⟨ 921 ⟩ : not more than 5.0%, except that Tablets labeled as gelatin-coated are exempt from this requirement.

Limit of 4-isobutylacetophenone— Using the chromatograms of the *Assay preparation* and the *4-Isobutylacetophenone standard solution* obtained as directed in the *Assay*, calculate the percentage of 4-isobutylacetophenone ($C_{12}H_{16}O$) in the Tablets taken by the formula:

$$10{,}000C(A / WI)(R_U / R_S),$$

in which C is the concentration, in mg per mL, of 4-isobutylacetophenone in the *4-Isobutylacetophenone standard solution; A* is the average weight, in mg, of a Tablet; W is the weight of Tablet powder taken to prepare the *Assay preparation; I* is the quantity, in mg, of ibuprofen per Tablet as obtained in the *Assay;* and R_U and R_S are the ratios of the 4-isobutylacetophenone peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively: not more than 0.1% is found per Tablet.

Residual solvents ⟨ 467 ⟩ **:** meet the requirements.
(Official January 1, 2007)

Assay—

Mobile phase, Internal standard solution, and *Standard preparation*— Prepare as directed in the *Assay* under *Ibuprofen*.

4-Isobutylacetophenone standard solution— Quantitatively dissolve an accurately weighed quantity of 4-isobutylacetophenone in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to 100.0 mL of *Internal standard solution*, and mix to obtain a solution having a known concentration of about 0.012 mg of 4-isobutylacetophenone per mL.

Assay preparation— Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1200 mg of ibuprofen, to a suitable container, add 100.0 mL of *Internal standard solution,* and shake for 10 minutes. [NOTE—Where the Tablets are coated, place an accurately counted number of Tablets, equivalent to not less than 1200 mg of ibuprofen, in a container, add an accurately measured volume of *Internal standard solution*, sufficient to obtain an *Assay preparation* containing about 12 mg of ibuprofen per mL, and about 15 glass beads, and shake until the Tablets are completely disintegrated.] Centrifuge a portion of the suspension so obtained and use the clear supernatant as the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨ 621 ⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for ibuprofen and 1.0 for valerophenone; the tailing factors for the individual peaks are not more than 2.5; the resolution, *R,* between the ibuprofen peak and the valerophenone peak is not less than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *4-Isobutylacetophenone standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for 4-isobutylacetophenone; the tailing factors for the individual peaks are not more than 2.5; the resolution, *R,* between the valerophenone peak and the 4-isobutylacetophenone peak is not less than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Separately inject equal volumes (about 5 µL) of the *Standard preparation*, the *Assay preparation*, and the *4-Isobutylacetophenone standard solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ibuprofen ($C_{13}H_{18}O_2$) in each Tablet taken by the formula:

$$100C(A / W)(R_U / R_S),$$

in which C is the concentration, in mg per mL, of *USP Ibuprofen RS* in the *Standard preparation; A* is the average weight, in mg, of a Tablet; W is the weight, in mg, of Tablet powder taken to prepare the *Assay preparation;* and R_U and R_S are the ratios of the ibuprofen peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively, or where intact Tablets were taken, calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in each Tablet by the formula:

$$(CV/N)(R_U / R_S),$$

in which V is the volume, in mL, of *Internal standard solution* used to prepare the *Assay preparation; N* is the number of Tablets taken; and the other terms are as defined above.

Auxiliary Information— *Staff Liaison* : Clydewyn M. Anthony, Ph.D., Scientist
Expert Committee : (MDCCA05) Monograph Development-Cough Cold and Analgesics
USP29–NF24 Page 1102
Pharmacopeial Forum : Volume No. 31(5) Page 1374
Phone Number : 1-301-816-8139

ANNEX 2

Disintegration Test of Tablets and Capsules European Pharmacopoeia Monograph

2.9. PHARMACEUTICAL TECHNICAL PROCEDURES

01/2005:20901

2.9.1. DISINTEGRATION OF TABLETS AND CAPSULES

The disintegration test determines whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium in the experimental conditions prescribed below.

Disintegration is considered to be achieved when:

a) no residue remains on the screen, or

b) if there is a residue, it consists of a soft mass having no palpably firm, unmoistened core, or

c) only fragments of coating (tablets) or only fragments of shell (capsules) remain on the screen; if a disc has been used (capsules), fragments of shell may adhere to the lower surface of the disc.

Use apparatus A for tablets and capsules that are not greater than 18 mm long. For larger tablets or capsules use apparatus B.

TEST A - TABLETS AND CAPSULES OF NORMAL SIZE

Apparatus. The main part of the apparatus (Figure 2.9.1.-1) is a rigid basket-rack assembly supporting 6 cylindrical transparent tubes 77.5 ± 2.5 mm long, 21.5 mm in internal diameter, and with a wall thickness of about 2 mm. Each tube is provided with a cylindrical disc 20.7 ± 0.15 mm in diameter and 9.5 ± 0.15 mm thick, made of transparent plastic with a relative density of 1.18 to 1.20 or weighing 3.0 ± 0.2 g. Each disc is pierced by 5 holes 2 mm in diameter, 1 in the centre and the other 4 spaced equally on a circle of radius 6 mm from the centre of the disc. On the lateral surface of the disc, 4 equally spaced grooves are cut in such a way that at the upper surface of the disc they are 9.5 mm wide and 2.55 mm deep and at the lower surface 1.6 mm square. The tubes are held vertically by 2 separate and superimposed rigid plastic plates 90 mm in diameter and 6 mm thick with 6 holes. The holes are equidistant from the centre of the plate and equally spaced. Attached to the under side of the lower plate is a piece of woven gauze made from stainless steel wire 0.635 mm in diameter and having mesh apertures of 2.00 mm. The plates are held rigidly in position and 77.5 mm apart by vertical metal rods at the periphery, a metal rod is also fixed to the centre of the upper plate to enable the assembly to be attached to a mechanical device

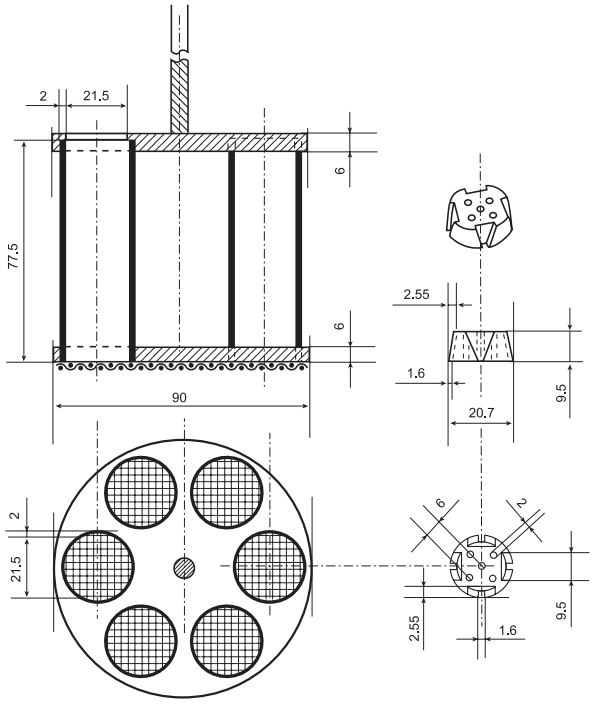


Figure 2.9.1.-1. – *Apparatus A*
Dimensions in millimetres

capable of raising and lowering it smoothly at a constant frequency between 29 and 32 cycles per minute, through a distance of 50 mm to 60 mm.

The assembly is suspended in the specified liquid in a suitable vessel, preferably a 1 litre beaker. The volume of the liquid is such that when the assembly is in the highest position the wire mesh is at least 15 mm below the surface of the liquid, and when the assembly is in the lowest position the wire mesh is at least 25 mm above the bottom of the beaker and the upper open ends of the tubes remain above the surface of the liquid. A suitable device maintains the temperature of the liquid at 35-39 °C.

The design of the basket-rack assembly may be varied provided the specifications for the tubes and wire mesh are maintained.

Method. In each of the 6 tubes, place one tablet or capsule and, if prescribed, add a disc; suspend the assembly in the beaker containing the specified liquid. Operate the apparatus for the prescribed period, withdraw the assembly and examine the state of the tablets or capsules. To pass the test, all the tablets or capsules must have disintegrated.

TEST B – LARGE TABLETS AND LARGE CAPSULES

Apparatus. The main part of the apparatus (Figure 2.9.1.-2) is a rigid basket-rack assembly supporting 3 cylindrical transparent tubes 77.5 ± 2.5 mm long, 33.0 mm ± 0.5 mm in internal diameter, and with a wall thickness of 2.5 ± 0.5 mm. Each tube is provided with a cylindrical disc 31.4 ± 0.13 mm in diameter and 15.3 ± 0.15 mm thick, made of transparent plastic with a relative density of 1.18 to 1.20 or weighing 13.0 ± 0.2 g. Each disc is pierced by 7 holes, each 3.15 ± 0.1 mm in diameter, 1 in the centre and the other 6 spaced equally on a circle of radius 4.2 mm from the centre of the disc. The tubes are held vertically by 2 separate and superimposed rigid plastic plates 97 mm in diameter and 9 mm thick, with 3 holes. The holes are equidistant from the centre of the plate and equally spaced. Attached to the under side of the lower plate is a piece of woven gauze made from stainless steel wire 0.63 ± 0.03 mm in diameter and having mesh apertures of 2.0 ± 0.2 mm. The plates are held rigidly in position and 77.5 mm apart by vertical metal rods at the periphery, a metal rod is also fixed to the centre of the upper plate to enable the assembly to be attached

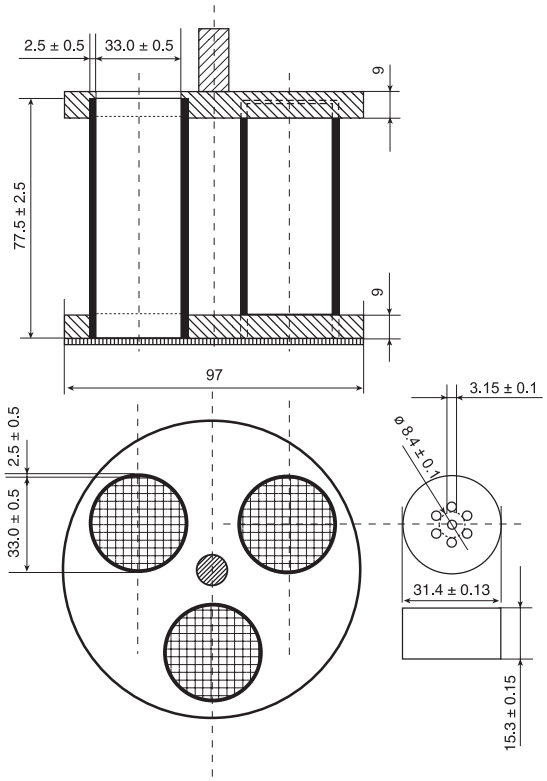


Figure 2.9.1.-2. – *Apparatus B*
Dimensions in millimetres

to a mechanical device capable of raising and lowering it smoothly at constant frequency between 29 and 32 cycles per minute, through a distance of 55 ± 2 mm.

The assembly is suspended in the specified liquid medium in a suitable vessel, preferably a 1 litre beaker. The volume of the liquid is such that when the assembly is in the highest position the wire mesh is at least 15 mm below the surface of the liquid, and when the assembly is in the lowest position the wire mesh is at least 25 mm above the bottom of the beaker and the upper open ends of the tubes remain above the surface of the liquid. A suitable device maintains the temperature of the liquid at 35-39 °C.

The design of the basket-rack assembly may be varied provided the specifications for the tubes and wire mesh are maintained.

Method. Test 6 tablets or capsules either by using 2 basket-rack assemblies in parallel or by repeating the procedure. In each of the 3 tubes, place one tablet or capsule and, if prescribed, add a disc; suspend the assembly in the beaker containing the specified liquid. Operate the apparatus for the prescribed period, withdraw the assembly and examine the state of the tablets or capsules. To pass the test, all 6 of the tablets or capsules must have disintegrated.

01/2005:20902

2.9.2. DISINTEGRATION OF SUPPOSITORIES AND PESSARIES

The disintegration test determines whether the suppositories or pessaries soften or disintegrate within the prescribed time when placed in a liquid medium in the experimental conditions described below.

Disintegration is considered to be achieved when:

a) dissolution is complete,

b) the components of the suppository or pessary have separated: melted fatty substances collect on the surface of the liquid, insoluble powders fall to the bottom and soluble components dissolve, depending on the type of preparation, the components may be distributed in one or more of these ways,

c) there is softening of the sample that may be accompanied by appreciable change of shape without complete separation of the components, the softening is such that the suppository or pessary no longer has a solid core offering resistance to pressure of a glass rod,

d) rupture of the gelatin shell of rectal or vaginal capsules occurs allowing release of the contents,

e) no residue remains on the perforated disc or if a residue remains, it consists only of a soft or frothy mass having no solid core offering resistance to pressure of a glass rod (vaginal tablets).

Apparatus. The apparatus (Figure 2.9.2.-1) consists of a sleeve of glass or suitable transparent plastic, of appropriate thickness, to the interior of which is attached by means of three hooks a metal device consisting of two perforated stainless metal discs each containing 39 holes 4 mm in diameter; the diameter of the discs is similar to that of the interior of the sleeve; the discs are about 30 mm apart. The test is carried out using three such apparatuses each containing a single sample. Each apparatus is placed in a beaker with a capacity of at least 4 litres filled with water maintained at 36-37 °C, unless otherwise prescribed. The apparatuses may also be placed together in a vessel with a capacity of at least 12 litres. The beaker is fitted with a slow stirrer and a device that will hold the cylinders vertically not less than 90 mm below the surface of the water and allow them to be inverted without emerging from the water.

Method. Use three suppositories or pessaries. Place each one on the lower disc of a device, place the latter in the sleeve and secure. Invert the apparatuses every 10 min. Examine the samples after the period prescribed in the monograph. To pass the test all the samples must have disintegrated.

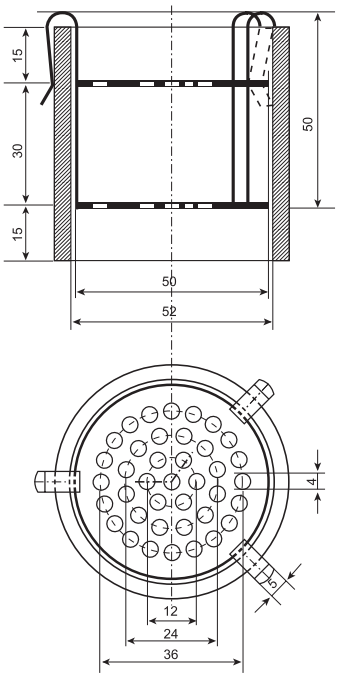


Figure 2.9.2.-1. – *Apparatus for disintegration of suppositories and pessaries*

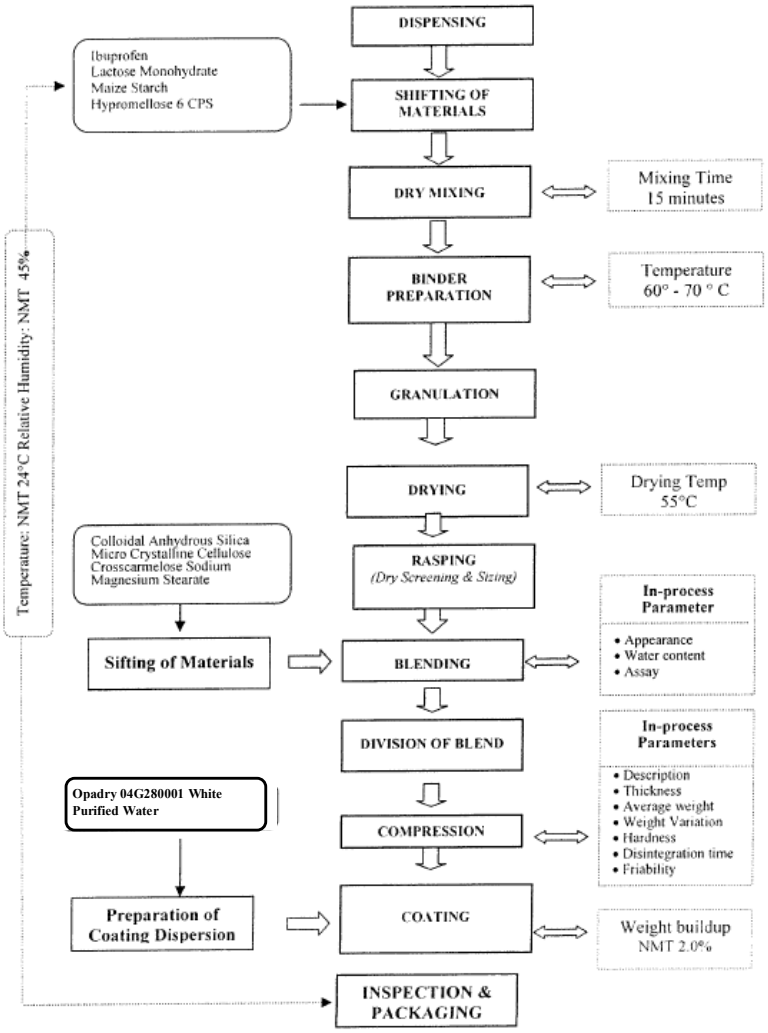
Dimensions in millimetres

METHOD OF OPERATION FOR VAGINAL TABLETS

Use the apparatus described above, arranged so as to rest on the hooks (see Figure 2.9.2.-2). Place it in a beaker of suitable diameter containing water maintained at 36-37 °C with the level just below the upper perforated disc. Using a pipette, adjust the level with water at 36-37 °C until a uniform film covers the perforations of the disc. Use three vaginal tablets. Place each one on the upper plate of an apparatus and cover the latter with a glass plate to maintain appropriate conditions of humidity. Examine the state of the samples after the period prescribed in the monograph. To pass the test all the samples must have disintegrated.

ANNEX 3

Manufacturing process



ANNEX 4

Manufacturing process Historical Data

BULK_BATCH	MANUF_DATE	API_PARTICLE_SIZE	WEIGHT_GAIN	DESINT_MIN	HARDNESS	DISSOL_AVERAGE	WATER_CONTENT
7LN076	26/12/2017	78,9	7,13	00:09:47	84	90	1
7LN077	26/12/2017	78,9	8	00:09:45	83	89	0,7
8AN072	12/01/2018	72	7,84	00:09:40	82	95	1
8AN073	12/01/2018	69,5	7,43	00:07:17	81	92	1
8BN083	19/02/2018	68,5	8,02	00:09:43	89	110	0,9
8BN084	19/02/2018	69	8,13	00:09:47	88	107	1
8CN078	23/03/2018	91,6	9,22	00:09:13	90	96	1,3
8CN079	26/03/2018	82,35	6,58	00:09:08	89	89	0,6
8DN088	20/04/2018	73,1	7,62	00:09:27	98	92	1,1
8DN089	23/04/2018	68,75	7,84	00:09:27	98	96	1,1
8DN090	23/04/2018	67,5	7,08	00:09:30	96	95	1,2
8DN091	26/04/2018	69	7,98	00:09:37	97	92	1,1
8EN089	21/05/2018	74,5	8,05	00:09:48	94	86	1,1
8EN090	21/05/2018	79	7,47	00:09:49	90	85	1,2
8EN091	21/05/2018	68,45	6,08	00:09:44	92	87	1,2
8FN125	29/06/2018	79	8,1	00:09:44	92	88	1
8FN126	02/07/2018	72	9,62	00:09:44	98	91	1,2
8GN007	03/07/2018	74	7,83	00:09:49	96	93	1,2
8GN001	03/07/2018	70,5	8,23	00:08:31	96	88	1,1
8GN002	03/07/2018	72	8,54	00:09:43	93	93	1,2
8GN008	04/07/2018	74	8,52	00:09:39	95	88	1,2
8GN009	05/07/2018	74	8,52	00:09:40	94	93	1,2
8GN010	05/07/2018	73,5	8,52	00:09:41	94	103	1,1
8GN011	06/07/2018	73,5	8,2	00:09:48	89	103	1,3
8GN145	27/07/2018	75,5	8,24	00:06:28	93	105	1,2
8HN070	03/09/2018	68	9,01	00:09:38	89	97	1,1
8HN071	03/09/2018	67	8,77	00:09:38	94	91	1,4
8JN088	17/10/2018	76	6,64	00:09:43	110	90	1,2
8KN096	27/11/2018	73,5	8,17	00:09:40	105	87	1,1
8KN097	27/11/2018	77	7,44	00:09:41	108	85	1,2
8KN098	27/11/2018	68,5	8,22	00:09:44	109	91	1,3
8LN087	19/12/2018	67,5	8,78	00:09:20	110	92	0,8
8LN088	19/12/2018	70,33	8,11	00:09:20	108	99	0,9
19AN006	31/12/2018	64,5	7,99	00:09:33	110	96	0,8
19AN005	02/01/2019	64	6,89	00:09:37	111	94	0,7
19AN007	02/01/2019	65,5	8,53	00:09:40	108	101	0,8
19AN057	10/01/2019	73	8,17	00:09:17	110	98	0,7
19AN058	10/01/2019	68	9,68	00:08:57	112	101	0,7
19AN059	10/01/2019	65	7,99	00:08:10	116	101	0,8
19AN060	11/01/2019	67	8,66	00:09:31	113	96	0,9

19BN058	11/02/2019	68,67	10,78	00:09:03	112	98	1,1
19BN059	11/02/2019	76	9,05	00:09:38	115	95	1
19BN060	11/02/2019	73	8,71	00:09:43	109	97	0,9
19BN167	28/02/2019	65	10,08	00:09:25	114	99	1
19BN168	28/02/2019	65	9,66	00:09:34	113	98	0,8
19CN051	06/03/2019	69	9,89	00:09:37	116	99	0,8
19CN097	25/03/2019	68	8,31	00:08:57	113	99	0,8
19DN112	02/04/2019	67,5	9,13	00:09:22	115	98	0,9
19DN111	24/04/2019	67	8,31	00:08:57	113	99	0,9
19FN004	06/06/2019	78	9,21	00:07:12	104	100	1,1
19FN005	06/06/2019	79,5	9,07	00:07:40	107	99	1,1
19FN006	06/06/2019	82	9,14	00:06:34	106	101	1,2
19GN044	08/07/2019	73	7,95	00:09:32	107	100	1,1
19IN051	05/09/2019	65,5	9,81	00:08:05	106	99	1,3
19IN052	06/09/2019	70	7,53	00:09:13	109	99	1,4
19IN053	09/09/2019	70	8,47	00:09:18	110	100	1,3
19JN141	28/10/2019	75	8,86	00:06:05	106	100	1,1
19JN142	28/10/2019	75	9,07	00:08:53	105	99	1

6.

REFERENCES

6. REFERENCES

1. CHMP/CVMP, 2012 Guideline on Real Time Release Testing (formerly Guideline on Parametric Release), European Medicines Agency.
2. European Medicines Agency, 2015 EudraLex - Volume 4, Annex 16: Certification by a Qualified Person and Batch Release, 1, European Comission.
3. European Medicines Agency, 2018 EudraLex - Volume 4, Annex 17: Real Time Release Testing and Parametric Release, European Comission.
4. CPMP/ICH, 2000 ICH Topic Q6A Specifications: Test Procedures and Acceptance. Criteria for New Drug Substances and New Drug Products: Chemical
5. General principles for Monographs on Finished Products (FPs) containing chemically defined active substances, 2017, EDQM.
6. New policy for dissolution and disintegration testing in Ph. Eur. Monographs, 2020, EDQM News.
7. CDER, 2017, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics
   Classification System Guidance for Industry, Food and Drug Administration.
8. M. Davit, Kanfer, Tsang, and Cardot, 2016, BCS Biowaivers: Similarities and Differences Among EMA, FDA, and WHO Requirements.
9. X Yu, Amidon, Polli, Zhao, 2002, Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions.
10. Yekpe, Abatzoglou, Bataille, Gosselin, Sharkawi, Simard and Cournoyer, 2017, Developing a quality by design approach to model tablet dissolution testing: an industrial case study.
11. CHMP, CVMP, 2017, Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action.
12. https://www.pharmamirror.com/knowledge-base/pharmaceutical-dictionary/immediate-release-drug-delivery-system/.
13. Zhang and Yu, 2004, Dissolution testing for solid oral drug products: Theoretical considerations.
14. CDER, 1997, Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms, Food and Drug Administration.
15. Ravendra Singh and Zhihong Yuan, 2018, Process Systems Engineering for Pharmaceutical Manufacturing.
16. Dokoumetzidis A, Papadopoulou V, Macheras P. 2006, Analysis of dissolution data using modified versions of Noyes–Whitney equation and the Weibull function.
17. J. Kochling, 2013, Approaches to the Investigation of Dissolution Testing Changes and Failures.

18. Markl and Zeitler, 2017, A Review of Disintegration Mechanisms and Measurement Techniques.
19. Potthast, Dressman, Junginger, Midha, Oeser, Shah, Vogelpoel and Barends, 2005, Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ibuprofen.
20. Yazdanian, Briggs, Jankovsky andHawi, 2004, The “The “high solubility” definition of the current FDA Guidance on Biopharmaceutical Classification System may be too strict for acidic drugs.
21. U.S. Pharmacopoeia, Ibuprofen Tablets Monograph.
22. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2009. Pharmaceutical Development Q8 (R2). Rockville, MD: Guidance for Industry.
23. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2011a. Quality Risk Management, Q9. Rockville, MD: Guidance for Industry.
24. European Medicines Agency, EudraLex - Volume 4, Good Manufacturing Practices.
25. Dumarey, Goodwin and Davison, 2015, Multivariate modelling to study the effect of the manufacturing process on the complete tablet dissolution profile.
26. Adeleye, Oyewo and Odeniyi, 2015, Effect of compression pressure on mechanical and release properties of tramadol matrix tablets.
27. CPMP/CVMP, 2001, Note for Guidance on Process Validation, European Medicines Agency.
28. Seo, Bajracharya, Hoon Lee and Han, 2020, Pharmaceutical Application of Tablet Film Coating.
29. Markl and Zeitler, 2017, A Review of Disintegration Mechanisms and Measurement Techniques.
30. Pharmaceutical Technology-11-02-2005, Volume 29, Issue 11, 2005, Improving the Physical and Chemical Properties of Ibuprofen.
31. Gabbott, Alhusban and Reynolds, 2016, The combined effect of wet granulation process parameters and Dried granule moisture content on tablet quality attributes.
32. Lobman K., et al, 2014, The influence of pressure on the intrinsic dissolution rate of amorphous indomethacin. Pharmaceutics.
33. Mallick, 2012, Correlation Between Compaction and Dissolution of Metoprolol Tartrate Tablets Prepared by Direct Compression using Different Polymers
34. Khadka, Ro, Kim, Cho, Yun and Lee, 2014, Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability.
35. Airaksinen, Karjalainen, Schevchenko and Westermack, 2005, Role of Water in the Physical Stability of Solid Dosage Formulations.
36. Ticehursta and Marziano, 2014, Integration of active pharmaceutical ingredient solid form selection and particle engineering into drug product design.
37. Ankit, Bilandi and Kataria, 2012, Tablet Coating techniques: Concepts and recent trends.

38. Müller, Brock, Knop, Zeitler and Kleinebudde, 2011, Prediction of dissolution time and coating thickness of sustained release formulations using Raman spectroscopy and terahertz pulsed imaging.

39. Silva, Webster, Chacra and Lobenberg, 2018, The Significance of Disintegration Testing in Pharmaceutical Development.

40. Zhao, Li, Shi and Drennen, 2019, Prediction of Dissolution Profiles From Process Parameters, Formulation, and Spectroscopic Measurements.

Tânia Freire | 2021

Mestrado em Engenharia Farmacêutica

Tânia Sofia Rodrigues Freire