UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCHAREST, DOCTORAL SCHOOL PHARMACY FIELD

TECHNOLOGICAL IMPLICATIONS ON THE QUALITY AND DEVELOPMENT OF A MODIFIED RELEASE TABLET

SUMMARY OF THE DOCTORAL THESIS

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Content

Introduction

The development of a new formulation is guided and strictly defined by the existence of methods of analysis of formulation tests carried out in the laboratory. The existence and/or ability to adequately test a formulation leads to the collection of solid, real, and useful data capable of measuring the outcome of a formulation test. Compendial analysis methods are restricted, but allow quality assessment for many pharmaceutical forms, i.e. medicinal substances.

In the technological development, the analytical development stage takes place simultaneously, starting from the need for quality control of the process, first of all, then of the intermediate, respectively finished products. The methods of analysis must provide sufficient evidence of:

- the sensitivity of a technological process to different technological variations,
- information regarding the capability of a technological process and the specific limitations of equipment – process – substance(s),
- repeatability,
- the impact of critical process parameters and the possibility of identifying work intervals with the aim of obtaining finished products in accordance with the expectations / requirements of quality, effectiveness and safety.

To meet the needs of patients and public health professionals, it is necessary to provide safe, effective and quality products. Measuring / determining the quality of medicinal products is only possible with the help of control methods in an integrated quality management system at each level.

The existence of a compendial monograph tends to facilitate the activity of technological development of new formulations with modified release, respectively of the standardization of control tests with an extended application in the pharmaceutical industry. Approving quality control methods as compendial takes a long time, being a coordinated process through working groups made up of specialists within government agencies.

Compendial monographs are few in number but preferred by the pharmaceutical industry from the point of view of certainty of application and ease of integration into a quality system. At this moment, the number of compendial monographs for the testing of solid pharmaceutical forms with modified release is much reduced compared to that of compendial monographs for traditional pharmaceutical forms.

The existence of a compendial test method for pharmaceutical forms with modified release does not exclude the application of a method developed in house, a method that may not generate similar/close results to the compendial method. In addition, there are also limitations in the development of in-house methods, limitations given by the existing patents of the original drugs.

The development of an in-house method for quality control when there is a compendial method must be adequately justified in the quality system, because it can be interpreted as a mask that protects most of the time the technological deficiencies of the developed generic formulation.

Developing a generic formulation is a real challenge, as it involves substantial financial and intellectual effort. For the success of such a challenge, the proposed experimental plan is important; plan that is based on experience and good ability to document experiments. The experimental plan can be strengthened by elements of risk analysis and statistics to streamline the documentation stages and define new test directions.

Experimental activity must be connected by appropriate means of measurement and control, because an unmeasurable experiment never leads to progress, and the results obtained must be integrated into pertinent conclusions.

In current laboratory practice, in vitro dissolution methods provide results that can indicate a traceability between series of medicinal products manufactured for the purpose of commercialization, but cannot identify variations in the therapeutic quality between series of the same type of product, variations generated by equipment, operator, working conditions or the use of different batches of excipients / active substances. Moreover, in vitro dissolution tests do not provide assurances regarding the biological traceability of the treatment, and the value of the similarity factor f_2 cannot be correlated with the possible biological activity of the drug. However, the existence of in vitro testing methods reduces the possibility of non-compliant pharmaceutical products appearing on the market.

Developing a generic formulation for Pentasa 500mg extended-release tablets and ensuring an adequate method for quality control is a source and alternative treatment for patients, as there is no generic drug registered to date for the original. The existence of several original or generic drugs for the same molecule, under the same therapeutic concentration or delivery mechanism, represents a huge advantage for patients and public health specialists.

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The supply of quality generic medicines for the health system is the basic condition for ensuring the continuity of treatments and limiting the risks in terms of ensuring the stocks of medicines in the field of public health.

The possibility of manufacturing for the purpose of commercialization for this developed product is high, because the development was carried out in full agreement with the basic requirements for ensuring the quality of the technological process, respectively the medicinal product.

In the development studies, several types of formulations and technological processes were followed in order to obtain representative data on the quality of the process and the finished product.

The main objective of the study was technological development and evaluation of the best technological process, feasible and reproducible for current manufacturing. The secondary objectives were to complete the technological study for the best formulation and to demonstrate documented the quality of the finished product in a storage time of one year and to study other technological possibilities of formulation by usual processes but modeling certain characteristics of the raw materials with the aim of obtaining industrially applicable results.

Through the present research, it is desired to develop a generic type formulation, test the quality of the technological process and the product obtained by using an effective quality control method developed starting from the compendial methods and the presentation of some practical aspects related to the manufacture in order to commercialize the developed medicinal product.

Many technological and qualitative studies have been carried out that highlighted the importance of the technological elements of the compression stage and the modulation of the physico-chemical properties of a tablet matrix with different failure mechanisms in close relation with the properties of the component ingredients.

1. Preparation of pharmaceutical oral solid dosage form with modified release mechanism

The multitude of pharmaceutical forms that contain the same active substances is proportional to the high need for the use of these substances in the treatment of patients with associated comorbidities or with the basic condition complemented by aspects such as: sensitivity to the active substance molecule, the manifestation of rare adverse reactions to the respective treatment (due to the genetic background).

In the current context, therapeutics take on "human" forms, because the genetic specificity is much studied and applied with the aim of reducing adverse effects, using appropriate dosage schemes and achieving results that want to follow a trend towards the ideal. A good example is given by one of the adverse effects of metamizole sodium (agranulocytosis) with an incidence of 1/million, but a higher incidence in the population of Nordic countries (a study carried out on a group of Swedish patients concluded an incidence rate of a little 1/1439 – when administered over a period of more than 2 months). [1]

The development of a drug treatment is done starting from the basic medical knowledge regarding the condition that is to be treated (the target), using the basic information of the most advantageous routes of administration that will indicate the optimal formulation required of the active substance molecule.

Modified release represents a superior technique for the preparation of pharmaceutical forms, based on scientific knowledge, which conditions the release of the active substance on some predetermined aspects (for example, the pH of the environment). This mode of release suggests that the rate of release of the active substance from the pharmaceutical form is different from rapid / normal release, but cannot be precisely described by a general mechanism.

2. The activity of research and development of new formulations

Research in the pharmaceutical industry has reached a high level as a result of general technological progress, and the available scientific literature provides consistent support for obtaining quality generic products despite the existence of patents. [2]

2.1. Laboratory scale development

Lab-scale formulation tests require solid documentation and preparation. The documentation phase is of particular importance, because a good knowledge of the characteristics of the active substance correlated with the medical aspects of the condition

constitutes the direction of the effective development of products that satisfy the needs of patients, respectively specialists in the field.

On a laboratory scale, simple tests are performed, and the equipment used is small in size with limited process monitoring possibilities. At this stage, practical and theoretical knowledge correlated with the specialist's ability to observe are extremely important.

Lab-scale formulation tests provide important information on:

- Quantitative and qualitative formula;
- Pharmaceutical form;
- The type of release profile for the pharmaceutical form;
- The main stages of a technological process.

2.2. Pilot scale development

In the pilot-scale development phase, the formula and the technological process are subjected to rigorous control tests, and the technological process parameters are carefully monitored in order to establish the criticality, respectively the operating limits.

The equipment used is capable of simulating processes close to those carried out in current manufacturing, and the variability of the test conditions is satisfactory compared to laboratory-scale tests.

The level of process control is clearly higher, the control steps during the process being defined, and the quality control performs tests in accordance with proposed quality specifications in order to implement satisfactory quality standards.

The results of quality control analyzes may determine adjustments in the formulation and manufacturing process. In the case of generics, the results are compared with the quality specifications of the product tested and chosen as a reference.

Completion of pilot-scale development studies involves establishing:

- The qualitative and quantitative formula of the developed medicinal product;
- The technological process (stages, technological parameters, critical process parameters);
- Control tests during the process;
- Quality specifications for intermediate and finished product.

Demonstrating the capability and robustness of the developed technological process is done through a validation stage. Technological validation involves documenting the way of

manufacturing and testing the manufacturing formula under similar conditions and reporting the results to predetermined quality standards.[1]

The studies carried out in this phase are critical, and the implementation of an adequate quality system ensures the preservation of the established quality attributes in the commercialization phase as well. Applying quality risk management concepts is a proactive way to identify, scientifically assess and control possible quality risks. [4]

2.3. Industrial manufacturing

Industrial manufacturing for the purpose of commercialization is carried out according to the marketing authorization and in accordance with the manufacturing authorization.

The technological process in industrial manufacturing is exposed to quality standards similar to those in the development stage, but the specifics of usage require the application of continuous improvement concepts and the increase of process performance.

3. Oral dosage forms containing mesalazine

A series of medicinal products available in the following pharmaceutical forms are sold in the market:

- Tablets (Dipentum 500mg, manufacturer UCB Pharma);
- Hard gelatin capsules (Dipentum 250mg, manufacturer UCB Pharma);
- Modified release tablets (Pentasa 500mg, manufacturer Ferring Pharmaceuticals);
- Gastro-resistant tablets (Salofalk 500mg, manufacturer Dr. Falk Pharma Gmbh.);
- Sachets with granules (product with modified release, manufacturer Ferring Pharmaceuticals).

4. Quality control

Quality control involves taking samples and testing them in accordance with the documentation drawn up for specifications and release procedures as well as the organization of documentation that confirms that the necessary relevant tests are carried out and that the materials are released for use in manufacturing and the finished products are released for marketing or distribution when their quality has been declared adequate. [1]

Quality control is not limited to laboratory activities, but must participate in all decisions that may affect product quality. The independence of quality control in relation to production is a fundamental element for its good functioning. [1]

Checking the conformity of quality attributes for a product involves evaluating the traceability of quality parameters, including their trend. The guarantee of the preservation of the effectiveness of the medicinal product is based on practical, quantitative determinations.

5. The working hypothesis and the general objectives

The present study proposes an analytical approach in the technological development of generic products (applied to the original product Pentasa 500mg modified-release tablets), starting from an in-depth knowledge of the physico-chemical characteristics for each raw material and the maximum use of properties for the purpose of quality modeling the finished product according to those of the original product. At the same time, the present study will analyze different technological processes specific to solid pharmaceutical forms with the aim of knowing the technological parameters with decisive implications in obtaining quality products.

6. Study of the active substance

In order to establish the optimal working conditions in order to preserve the quality attributes of the medicinal product, the impact of environmental factors in the working area on mesalamine was studied, starting from the recommendations of the European Pharmacopoeia. The European Pharmacopoeia recommends keeping the raw material in well-closed containers, away from light and moisture. [5]

Behavioral tests were performed in ambient working conditions on:

- active substance;
- intermediate product (according to the formulation subject to validation): granule (mesalazine and polyvinylpyrrolidone), compression mixture and tablets;
- Mesalazine solution/suspension in purified water (useful assessment for equipment, utensil and space cleaning steps).

Ambient conditions in the work area:

- Relative humidity: maximum 65%;
- Artificial light;
- The temperature: 22 ± 2°C.

The color of the raw material is faint pale pink, a color that is also printed on the finished product, and according to the manufacturer's analysis report, the product is described in terms of color as pale pink to pale brown. In this case, it can be assumed that

the color shift of the bulk / finished product has no impact on product attributes such as: safety, efficacy, identity, concentration and quality.

The results of the stability study of the active substance, under working conditions, indicate that light is an influencing factor of the quality of the product in terms of appearance.

As a result of the observations, the following preventive measures are required:

- Throughout the development process, avoid prolonged exposure of the active substance, intermediate products and the finished product to light;
- Quarantine storage for the finished product and intermediate products will be carried out only with adequate protection measures against the action of light. It is recommended to cover polyethylene bags with black polyethylene film or store in opaque containers;
- It is recommended that the finished product be subjected to the primary packaging operation as soon as possible after its processing.

In addition to the study of the environmental behavior of the active substance (mesalazine), the stability study with excipients was also carried out by a differential calorimetric method, with the aim of an appropriate selection of excipients. After studying the recorded diffractograms, it is found that there are no major changes in the DSC graphs of the mixtures of mesalazine with the proposed excipients. Thus, the proposed excipients can be used in the development of medicinal formulas with mesalazine as an active substance.

7. Study of the reference product

The chosen reference product is Pentasa of 500 mg modified-release tablets, manufactured by Ferring Pharmaceuticals GmbH, Germania.

Qualitative composition of the reference product: microcrystalline cellulose, ethylcellulose, magnesium stearate, talc, povidone.

The reference product is packed in: primary packaging: OPA Al blister and closed with aluminum foil, secondary: cardboard box and leaflet.

Parameter	Result
Description	Round tablets with a midline, light gray in color and pale pink to pale brown marbling, respectively embossed text on both sides: 500 on one side and PENTASA on the other side.
Height	4.23 mm
Diameter	13.6 mm
Hardness	111 N

Parameter	Result
Average mass	749.7 mg
Disintegration	Maximum 5 seconds (tablet opened in granules)

Table VII.1. Results of pharmaco-technical analyzes of the reference product.

8. Development of analysis methods

The quality control stages during the process have a preventive role, being result-generating stages with a strong impact on quality. Each critical stage of processing and packaging must have adequate quality control to ensure the quality of the manufactured product. Quality control tests are defined and established from the product development phase, when they can be adequately documented and characterized.

9. Quality of raw materials

The raw materials used in the manufacture of medicines for human use must meet specific criteria defined in the legislation in the field. They must be manufactured by authorized manufacturers who have implemented a functional quality management system capable of generating products of consistent quality.

The main quality criteria that must be met by a raw material are:

- The raw material must be manufactured under controlled and documented conditions, according to the requirements of Part 2 of the Good Manufacturing Practice guide, June 2017 edition (developed by the National Agency of Medicines and Medical Devices);
- Knowledge of the supply chain of the producer of raw materials and the qualification of suppliers / producers;
- Application of validation principles for manufacturing and testing activities, respectively qualification;
- Carrying out stability studies to demonstrate the allocated validity period;
- Analyzes for elemental impurities;
- Declarations for: sources without genetically modified organisms, pesticides, insecticides or herbicides, respectively processes without irradiation;
- Another important aspect is the definition of the distribution chain from the producer of raw materials to the manufacturing unit of the medicinal product (environmental transport conditions are also important).

10. Development of a technological process

10.1. Formulation study

The aim of the development activity is to create a solid oral pharmaceutical form, in the form of prolonged-release tablets with a Mesalazine content of 500 mg/tablet. Formulation followed qualitative description and technological implications in making tablets with extended release profile. In the pharmaceutical development, the choice of a formulation with a reduced number of excipients, a simple manufacturing process and as easy to control as possible was considered.

In order to obtain some technical details, behavior of the active substance in a simple technological process, initial formulation tests were carried out, which assume:

- direct mixing process, followed by compression;
- wet granulation and homogenization with hydrophilic matrix former;
- wet granulation and coating with functional film in order to know optimal formulation techniques;
- wet granulation and compression.

10.2. Intermediate technological studies

As a result of the optimistic results provided by the correlated tests in Formulas 20 and 21, it is necessary to study the behavior on equipment with specific features of industrial manufacturing. At this stage, 3 technological formulations were studied based on a technological process of wet granulation, granule drying, homogenization and compression.

10.3. he conclusions of the technological studies

Numerous technological research studies totaling 24 distinct tests were carried out, and for certain formulations variations from the basic test were carried out within the same test with the aim of obtaining complex data capable of generating solid and important conclusions on the direction of study.

The technological development study included a significant number of tests to identify a granulation technology, these included:

- Active substance granulation with Kollidon 30 aqueous solution;
- Granulation active substance and Tablettose 80 with aqueous suspension of Starch 1500;
- Active substance granulation with aqueous suspension of Starch 1500;
- Active substance granulation with Carbopol 971 powder.

The studies regarding the creation of a tablet-type pharmaceutical form with modified release involved addressing the following aspects:

- Making a hydrophilic matrix type tablet (based on hydroxy-propyl-methyl-cellulose);
- Realization of a pharmaceutical form such as tablet support / vehicle for granules covered with a functional film;
- The production of a tablet by wet granulation technology.

Technological studies were extended with the aim of adequately documenting the process steps and collecting a significant number of results that were used to strengthen decisions regarding the selection of the final formulation.

Through the technological studies, the dependence relationships between the technological parameters and the pharmaco-technical characteristics of the intermediate / finished product, the influences of some variations in the quality of the granules on the dissolution, hardness and height parameters were characterized.

Porosity and central absorption studies inside the tablet were demonstrated by formulation 16. In this test, the impact of elastic excipients like cellulose with high swelling capacity in aqueous media is studied with important consequences in the dynamics of the granular dissolution process of tablets.

The selection of cellulosic grades with a diluting role in the formulation placed the dissolution parameter in a much lower area, which was also indicated by the disaggregation test of the tablets.

Formulation 20 uses an amorphous diluent base, water-soluble, but with high compaction capacity that prints a long dissolution profile for the pharmaceutical form. By comparing the composition of formula 20 with that of formula 16, the impact of the type of diluent used is clearly defined.

The selected formulation is a simple one with a technological process based on wet granulation of the active substance. Satisfactory results were achieved as a result of the combination of the following factors:

- ✓ High compressibility (granules and excipients);
- ✓ Good intragranular and intergranular adhesion forces;
- ✓ btaining a tablet with reduced porosity (see the microscopic images presented in chapter 3);
- ✓ Lack of disaggregating components.

11. Conclusions and personal contributions

11.1. Conclusions

The technology study for the development of a solid pharmaceutical form in the form of a modified-release tablet evaluated the following technologies:

- ✓ Direct compression of a mixture of mesalazine and excipients specific to solid dosage forms (lubricants, diluents).

The mixing-compression technological formulation was not possible due to the lack of free flow of the mixture, this being totally influenced by mesalazine.

- ✓ Wet granulation – compression.

The qualitative implications of the wet granulation process were evaluated separately, then together with the compression step. 23 formulas that had a wet granulation stage were studied.

Wet granulation was carried out with polyvinyl pyrrolidone (Kollidon 30 commercial grade), Carbopol 971, respectively pregelatinized starch (Starch 1500 commercial grade). Granules obtained using only Kollidon 30 binder and mesalazine demonstrated good compressibility and intense intergranular adhesion. To increase the dissolution capacity of the active substance in the modified-release tablet, pregelatinized starch was introduced in the wet granulation step. Due to its hydrophilic nature, the permeability of the tablet was significantly improved, respectively the dissolution of mesalazine.

The wetting agent, Starch 1500, introduced in the wet granulation phase (intragranular), loses a lot of its permeability capacity compared to its introduction in the homogenization phase (extragranular), a fact demonstrated by the increase in the similarity factor for the first 100 minutes of dissolution.

The size of the mixture granules totally influences the compression process by requiring the application of lower compression forces for a mixture with large granules (0.9-0.71mm) and for a mixture with small granules (0.5-0.2mm) it is necessary to apply a force almost 2kN higher. This fact is due to the intense fractionation of the mixture and the increased need for intergranular adhesion, but with significant consequences on the quality of the tablet obtained. Tablets obtained from the mixture containing small-sized granules (0.5-0.2mm) are more than 5 times more friable than those with large-sized granules (0.9-0.71mm). Also as a result of a reduced compaction of the granular mixture with dimensions of 0.5-0.2mm, the height is higher by about 1mm.

Wet granulation with the methacrylate binder proved difficult to control for the following reasons:

- The amount required to obtain dense and resistant granules for the drying stage is approximately 5%; quantity established by practical observations and literature data;
- Wet calibration of granules is difficult due to the gummy nature of the intermediate product;
- Drying of wet granules based on methacrylate (carbopol 971) is laborious, long, or difficult due to the gelling behavior. In the initial phase of fluidbed drying, it is necessary to apply a slightly high temperature with increased air flow to prevent sticking to the base of the vessel, then adjust the 2 parameters shortly after the formation of the granules. The internal drying of the formed granules is limited by the external film layer formed, thus a long drying period at low temperatures is required.
- Dry calibration of granules is done at low speeds and after drying below 0.4%. Despite the fact that the moisture content of the dry granules is low, calibration is difficult because the granules have an elastic behavior and stick to the sieve meshes.

✓ Homogenization

Different excipients were used with the functional role of:

- Surface (magnesium stearate) and granular (colloidal silicon dioxide, talc) lubrication. These 3 excipients facilitate the compression process itself.
- Diluents: varieties of microcrystalline cellulose and lactose monohydrate. Microcrystalline cellulose greatly increases the disaggregation effect and enhances the dissolution rate. The lactose monohydrate used generates tight intergranular bonds and good compaction of the tablet.
- Humectants: pregelatinized starch (Starch 1500).
- Matrix formers: modified cellulose derivatives (various grades of hydroxypropyl methylcellulose). The 2 grades used showed a linear failure profile and limited to a failure profile over a duration of 8 hours.

✓ Granules coating

Granulation studies were carried out using the binder Carbopol 971 powder – 3 granulation studies. Granules based on Carbopol 971 powder showed a hygroscopic tendency as a result of the specific properties of the granulating agent.

Coating of the granules was carried out with:

- ✓ Eudragit NE30D and Methocel E5 LV Premium (with role of pore former) – 1 single study. The coating process with the mixture of these 2 agents is difficult, and the technological losses recorded were much higher than estimated.

This type of coating agent in combination with the pore former did not achieve satisfactory results in terms of the stability of the coating layer.

- ✓ Surelease E-7-19040 Clear aqueous dispersion – 2 studies with different concentrations in coating agent.

The film applied on the surface of the granules failed to provide the expected results, because their degree of coverage was greatly reduced by the irregular surface of the granules and the high roughness of the surfaces.

Through the microscopic studies carried out on the coated granules, numerous areas without a functional film were identified, and through the dissolution studies (on the coated granules) the inefficiency of the coating process of the uneven granules obtained by: wet granulation, drying and dry calibration was demonstrated.

For an additional loading of the granules with the aim of a possible uniform coating, the tablet pharmaceutical form could no longer be realized, because the mass of the coated granules became very high - a lot of excess coating agent is needed.

11.2. My own contributions

Knowledge level contributions consist of:

- Definition on a documented basis of the relationship between the technological parameters of the compression process and the quality of the finished product,
- Importance of determining the granulometry of the compression mixture, which contains granules through a wet granulation step, and maintaining it when changing the technological scale of the manufacturing process in order to obtain a traceability of the results of the technological development study.
- Documenting the quality of the excipients and their role in obtaining compacts with a dense core, reduced porosity and controlled hydrophilicity.
- Demonstration of the limitations of a technological process of coating some granules in a fluidized bed and the main control aspects of the technological parameters.

All these knowledge contributions, studied in a unitary manner, made it possible to develop a solid pharmaceutical form with modified release without using a matrix forming

agent or porous/membrane filming agent. The modified release process being modulated by the solubility of mesalazine and the high compaction qualities of the mixture used in order to reduce the porosity of the tablet.

The final result has a practical value, because the technological process developed and characterized was validated, and the product quality was evaluated for a year.

List of published papers

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2. Cătălin Donea, Daniela Elena Popa, Anne-Marie Ciobanu, Petru Crăciun, Doina Drăgănescu, Mircea Hîrjău, George Traian Alexandru BurceaDragomiroiu, Dumitru Lupuliasa. Evaluation of the granulometry impact of the compression mixture in the formulation development of tablets. Farmacia journal, Vol. 70,6, 2022.

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