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Development and in vitro evaluation of topic semisolid pharmaceutical preparations and in vitro - in vivo correlation

PhD THESIS SUMMARY

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Introduction

The proposal of a classification system useful in the comparative analysis of topical semisolid products, reference and experimental formulations, future generics was a new approach, facilitating the evaluation and authorisation procedures (*Topical Drug Classification System,* TCS; Shah VP et al, 2015, 2016). The biopharmaceutical parameters solubility and permeability, on which the abbreviated BCS classification system is based (*Biopharmaceutics Classification System*), have been replaced with degrees of similarity for composition (qualitative and quantitative, Q1 and Q2), respectively for microstructure (Q3). In other words, the central element is the result of a comparison, not the characteristics of the active substance. If reverse engineering approaches are needed to analyze the Q1/Q2 similarity, the use of IVRT was proposed to assess a possible impact of the internal arrangement of the semisolid matrix.

Biowaiver procedures can only be applied in cases where in *vitro* performances are similar (TCS classes 1 and 3) and differences in composition can only be accepted upon presentation of sound scientific arguments on the lack of influence on permeation and biological barrier penetration (TCS class 3).

The choice of the research theme was determined by the evolution of *in vitro* performance tests from analyses of variations to key components of the biowaiver procedures, on the one hand, and by the need to validate the classification principles specific to the TCS system, on the other hand.

The importance of the theme and the experimental plan is given by the continuous extension of the scope of IVRT methodologies, from the well-defined context of variations (abbreviated SUPAC in FDA guidelines, eng. *Scale Up Post Approval Changes*; FDA, 1997) to comparisons of multisource products having a simple vehicle (mixture of two well-defined and easily physico-chemically characterized components) or complex (e.g. emulsion systems with partial dissolution of the active entity and specific distribution between internal and continuous phases). While *in vitro* studies using artificial membranes represent an extreme simplification of the biological context, elucidating the interrelationships that determine the release rate represents an opportunity for development and rapid authorization of generic alternatives, by avoiding clinical endpoint studies.

The novelty of the theme is the integration of TCS classification principles, which allow greater flexibility in the selection of qualitative and quantitative composition for a generic product, invalidating the strict requirements of Q1 and Q2 similarity and using *in vitro* release as a central tool in the analysis of microstructural differences. The approach is

modern from two points of view: i) the characteristics of the TCS class 1 coincide with the recommendations of the regulatory authorities in the field to reduce the biopharmaceutical risks for generic semisolid pharmaceutical forms by ensuring the similarity triad Q1-Q2-Q3; ii) gradual acceptance of differences of more than 5-10% between the quantities of excipients in the semisolid matrix, corresponding to TCS class 3. The fact that the hypothesis issued in 2015 is confirmed by guidelines published between 2018 and 2022 (EMA, 2018; The FDA, 2022a; 2022b;2022c), even without explicitly mentioning TCS, demonstrates **the relevance of the research topic.**

The research hypothesis was that, through appropriate development and validation, the IVRT methodologies can be adequately discriminatory and predictive for the rapid, reproducible and (bio)relevant assessment of topical semisolid formulations. In reality, this is the central assumption of the TCS classification system. Non-similarity of *in vitro* performance may signal therapeutic non-equivalence, and equivalence of *in vitro* release rates may ensure the absence of clinically significant differences between two multisource products.

The scientific objectives set out in the research theme were: i) the appropriate choice of compendial experimental devices (with known hydrodynamic design and characteristics); ii) selection of optimal experimental parameters to ensure compliance with Higuchi diffusion model requirements and considering the specificity of creams containing 5% acyclovir; iii) demonstration of the sensitivity, selectivity and specificity of the IVRT method; iv) extended validation by analysis of formulations with known variations in composition; v) the assessment of the discriminatory character by applying the methodology in the study of the inter-batch variability of the reference product and of the performance differences for multisource generic products; vi) the development of a group of formulations illustrating different TCS classes and the validity of its scientific principles; vii) analysis of *in vitro* release rate - microstructural characteristics relationships and estimation of consequences on *in vitro* performance for developed experimental formulations.

The methodological approach was selected based on the recommendations available in two fundamental documents for the research topic's domain: the post-approval changes assessment guideline issued by FDA in 1997 (SUPAC-SS) and the compendial chapter 1724 on performance testing for semisolid products, originally published in the second supplement of the United States Pharmacopoeia (USP, 2013).

The choice of vertical diffusion cells was based on the large number of individual

test devices available, which ensured adequate control of experimental variability. Current criteria have been applied to select the receiving environment and artificial membrane interfaces, so that the release rate to represent a critical quality attribute.

The developed methodology was applied for comparative analysis of *in vitro* performance for two groups of formulations. The first group consisted of pharmaceutical equivalent multi-ource semisolid products, generic formulations and official references from the United States of America and Europe. The discriminatory character of the IVRT for differences in qualitative composition has been demonstrated, even in the absence of detailed information on quantitative composition.

The principal component analysis (PCA) confirmed the non-inert character of some excipients by the major impact on the similarity of *in vitro* behaviour.

The experimental plan due to having an **interdisciplinary character** was implemented through the collaboration of several working groups, partners in the validation project of the TCS classification system. The experimental formulations were manufactured following the good manufacturing practices within a local medicinal products manufacturer. Collaboration with this manufacturer also allowed quality control and real-time stability studies and accelerated conditions. The collaboration agreements between the Center for Drug Sciences and representatives of the European pharmaceutical industry allowed the expansion of the sample of analysed multisource products and consultations on the relevance and applicability of the research. Last but not least, the group of researchers involved in the validation of the TCS system included experts in the field and members of the PQRI, who regularly reviewed the results presented below.

The research carried out is currently **being continued by** including in the experimental plan several types of pharmaceutical forms, containing medicinal substances with structural differences, physico-chemical properties, dose and routes of administration. Paradoxically, **one of the limitations of the research** is the simplicity of the experimental protocols and the proposed approaches, starting from the validity of the TCS principles.

Chapter 4. Development and validation of the *in vitro* release method adapted to the particularities of the cream containing 5% acyclovir

An *in vitro* release method specific to topical cream semisolid formulations containing 5% acyclovir has been developed. The selection of vertical diffusion cell as experimental devices was done through the evaluation of authorised products and the use of equipment described in Chapter 1724 of the United States Pharmacopoeia. Preliminary studies took into account the variability of experimental data, the identification of sources

of error and sensitivity to microstructural factors.

The development phase included determination of acyclovir solubility, stability during testing and adsorption potential on hydrophilic membrane interfaces. In order to validate the methodology, experimental formulations were prepared, the composition of which was chosen according to the provisions of the in force guidelines (variations in the concentration of the active substance and excipients, inert or non-inert according to the TCS dichotomy). Further evaluations were carried out by testing the reference product, analysing the discriminatory character of the compositional variations of the authorised formulation, as well as the inter-batch consistency of the *in vitro* performances.

The IVRT method was sensitive, selective and specific according to currently available validation criteria. Linear dependence has been demonstrated between the theoretical concentration of acyclovir (25-100 mg/g) and the *in vitro* release rate or cumulative quantities yielded at the end of the test interval. Correlation coefficient values were higher by considering the concentration square root parameter, thus confirming the aggregation state of the analyte, partially suspended in the semisolid matrix. The study confirmed its discriminatory nature in relation to the microstructural impact of a non-inert excipient.

The increase of the concentration of propylene glycol, known to promote penetration and permeation of acyclovir after local skin administration, resulted in increased diffusion resistance due to altered matrix interactions.

The Q1 non-similarity found for the reference product registered in the United States and Europe induced distinct *in vitro* release profiles. The absence of three excipients has been shown to cause microstructure changes, which are the source of diffusion rate differences. Last but not least, for the same qualitative composition, remarkable reproducibility of *in vitro* performance (inter-batch consistency) was observed.

Chapter 5. Implementation of the *in vitro* release method in the study of multisource products. Analysis of the Q1-IVRT relationship

The next step of the experimental plan was the application of the previously developed and validated IVRT method for the evaluation of a set of topical multisource semisolid cream products containing 5% acyclovir. One of the purposes was to analyze the relationship between the Q1 similarity and *in vitro* performance, even in the absence of quantitative composition data. The results obtained were fully published in the article entitled: Does European marketed acyclovir 5% cream products similar? Comparison with EU and US reference product, published in Drug Development and Industrial Pharmacy

magazine (2021:47(6): 990-1000, (Miron DS, 2021a).

The previously developed and validated IVRT methodology was applied for the comparative assessment of a group of 22 multisource cream products containing 5% acyclovir.

Similarity of performances was analyzed by applying the procedures and criteria recommended in the US-FDA SUPAC-SS guideline (1997). Available data on the qualitative composition have been inventoried and compared to those specific to the reference products. A grouping of components was also performed by considering the potential influence on the solubility of the active substance, the microstructural arrangement or the permeability through the biological interface, as a transposition of the TCS specific inert – non-inert classification.

Procedures specific to the principal component analysis were applied, which confirmed the discriminatory character of the *in vitro* release tests. The Q1-IVRT relationship, demonstrated both in the case of a dichotomous classification (which considers the presence or absence of an excipient), but also by grouping excipients into categories based on their structural or functional role, validates the TCS hypothesis and allows the extension of the limits of application of *in vitro* options for bioequivalence demonstration, without increasing the risks of therapeutic non-similarity.

Extending the limits for defining the Q1-Q2 similarity and maintaining comparative evaluation criteria for in vitro performance, even with extreme simplification of the in vivo use context (pseudo infinite dose, sink and occlusive conditions, inert artificial membrane), can facilitate the development of generic products and reduce therapy costs, while guaranteeing access to health services.

Chapter 6. Development and formulation of creams containing 5% acyclovir. Study of the relationship between composition, microstructure and *in vitro* performance

This last chapter describes the development of topical cream-like semisolid formulations containing 5% acyclovir by integrating experimental data and using the methodological approaches described above. It is an example of selection of qualitative and quantitative composition, method of preparation and sources of raw materials, using as a decision tool the similarity or in vitro performance differences analysed by IVRT. The principles specific of the classification system of topical drug products were applied (TCS; Shah VP et al, 2015; 2016) and there were considered the three levels of variation described by the SUPAC-SS guide (SUPAC-SS, 1997) for predicting possible in vivo

consequences. The followed steps made it possible to elucidate the influence of each factor and to understand how the semisolid matrix plays the role of a pharmaceutical vehicle for local administration on the skin.

The results were published integrally in the article entitled: Rheological and in vitro release measurements of manufactured acyclovir 5% creams: confirming sensitivity of the in vitro release, in the academic journal Pharmaceutical Development and Technology 2021;26(7): 779-787, https://doi.org/10.1080/10837450.2021.1945625 (Miron DS et al, 2021b).

Based on the relationships between the qualitative composition of creams containing 5% acyclovir and in vitro release profiles, including consideration of the results of PCA procedures, experimental formulations illustrating the three levels of variation described by the SUPAC-SS guide and the four classes of the TCS system have been developed and prepared. Using a standard (authorized) pharmaceutical formulation, modified by the addition of a critical excipient (propylene glycol), various controlled variations in qualitative or quantitative composition and manufacturing process parameters were applied. The resulting creams were included in three subgroups, compared successively with the internal reference.

A number of physico-chemical tests were applied to assess the quality, stability profile and microstructural characteristics (determination of the type of dispersion system, the state of aggregation of the drug substance, the morphology and size of suspended particles).

For the study of rheological behavior, oscillatory and rotational analyses were used, performed at two temperatures relevant for the storage of products, respectively for local application to the skin. In addition, a procedure was applied to determine the influence of gradual warming on the viscoelastic response specific to semisolid matrices.

The results obtained confirmed the discriminatory nature of the *in vitro* test profiles compared to the similarity or differences Q1-Q2-Q3. Changing the parameters of the preparation process had little structural impact. The rheological behaviour of the four experimental formulations was similar, with values of parameters characteristic of the viscoelastic linear region and comparable shear stress. Differences in the areas under the curve specific to the tixotropy test were observed, directly proportional to the *in vitro* release rate.

The quality parameters of the raw materials had a significant influence, generating non-similarity of in vitro performance. The use of alternative sources for inert or non-inert

excipients has been illustrated in the context of TCS Class 2, where the similarity Q1 - Q2 does not allow the application of biowaiver procedures. Microstructural differences, signalled by the IVRT discriminatory methodology, induce major risks of non-bioequivalence.

Controlled variations in the quantitative composition confirmed the previously formulated hypothesis that IVRT can be a sensitive, selective and specific methodology in relation to excipients that influence permeability. Experimental data demonstrated that *in vitro* release may reflect changes in interactions within the semisolid matrix generated by propylene glycol. An inverse proportionality relationship was observed between the shear stress (estimator of the spreading capacity, which decreases by increasing the concentration of this critical excipient from 10 to 40%) and the *in vitro* release rate.

7. Conclusions and personal contributions

Conclusions

The experimental plan of the thesis was designed based on the principles of the *Topical drug Classification System* (TCS), according to which an *in vitro* release methodology, properly developed and validated, can become a useful tool in the evaluation and authorisation of this type of special pharmaceutical formulation, alone or in combination with other physico-chemical or microstructural comparative tests. Similarity of *in vitro* performance allows the application of biowaiver procedures, by characterising the differences between a reference and a generic product and correctly estimating the potential clinical consequences.

The selection of the experimental device model was preceded by preliminary studies comparing several types of diffusion cells, in line with the descriptions available in the compendial chapters. The evaluation of the results took into account the reproducibility of the experimental data and the sensitivity to known differences in the qualitative composition between two medicinal products authorised based on comparative clinical endpoint studies. Differences in geometry and hydrodynamic parameters influenced the values of *in vitro* release rates without changing the discriminatory character. The option for vertical diffusion cells was justified by the existence of reports in the literature confirming the feasibility of developing *in vitro in vivo* relationships, the experience gained in the Centre for Drug Sciences (including in the validation process of TCS) and the availability of a large number of individual test posts.

Operational parameters were adapted to the characteristics of topical semisolid products containing 5% acyclovir by determining the solubility of the drug substance, the

hydro-alcoholic type receptor environmental stability profile and the inertia or lack of adsorption potential of the inert artificial membranes. To validate the methodology, experimental pilot formulations were prepared, representing the target concentration and variations of 50 and 200% of the theoretical active entity content. They were used to demonstrate the sensitivity, specificity and selectivity of the IVRT methodology (dose discrimination). Complementary studies have demonstrated robustness and reproducibility. The extended validation included two steps. First, controlled variations in quantitative composition were implemented (minor for cetylstearyl alcohol, as an inert excipient, or major, for propylene glycol, as a non-inert excipient, known to promote percutaneous absorption). The results demonstrated complex relationships between the nature and quantity of these components, the internal arrangement of the semisolid matrices generated and *the in vitro* performance. Testing of the available reference product in two non-similar but therapeutically equivalent Q1 compositions was considered as evidence of additional selectivity or microstructural sensitivity. At the same time, a remarkable inter-batch reproducibility of the reference product authorised on the European market was demonstrated through the study of five batches with considerable age differences.

The IVRT methodology developed and validated according to the criteria recommended by the in force guidelines was applied on a group of multisource cream products containing 5% acyclovir. The study allowed the use of principal component analysis procedures where the similarity or difference of Q1 was correlated with the outcome of the *in vitro* comparative performance analysis. The grouping of excipients based on the potential impact on the pharmaceutical vehicle`s properties or on the permeability through the biological barrier confirmed the validity of the TCS classification principles. Components considered inert have limited impact on penetration and permeation through the skin, but can significantly influence the internal structure of the matrix, its response to external factors (mechanical stress, temperature changes) and, consecutively, diffusion profiles through artificial inert membranes. On the other hand, non-inert excipients play a different role depending on the context. In topical formulations they can manifest themselves as solubilizing agents, alter the distribution between the component phases of a dispersed system and influence the intensity and even the nature of the interactions that determine the specific semisolid behavior. The obtained results confirmed the sensitivity of the IVRT methodology for this type of influences. The biorelevance of *in vitro* release profiles is not invalidated by the use of an inert membrane.

The relationships between composition (qualitative and quantitative), rheological

behaviour and *in vitro* performance were analysed in the context of the development and preparation of experimental cream formulations containing 5% acyclovir. The studies carried out made it possible to assess the impact of some controlled variations, correlated with the three levels described by the SUPAC-SS guide and illustrating different classes of the TCS system. The protocol can be applied for the selection of an optimal formulation in the research and development process, after adequate identification and detailed characterization of a reference.

The advantages of the proposed methodological approaches derive from the demonstration of Q1-Q2-Q3-IVRT relationships or correlations. Experimental data are arguments for the gradual extension of the limits of application of *in vitro* options for bioequivalence demonstration, where the central element is a simple, reproducible and (bio)relevant test. The impact of biowaiver procedures on the pharmaceutical industry can be major, not only from the perspective of generic authorisation. It can be estimated that the optimisation of any authorised topical semisolid formulation is limited by the current regulatory framework according to which the complexity of the products and the reactivity of the biological barrier justify the use of clinical studies as the standard method to demonstrate safety and efficacy. Thus, the main disadvantage of TCS-based approaches is the conservative attitude of the authorities, their reluctance to accept the assessment of a complex interaction through a simple test.

Evaluation of the relationship between composition and *in vitro* performance, respectively the accuracy increasing of predictions made through PCA procedures, makes it necessary to extend this experimental plan by including in the future several types of active entities, with differences in physico-chemical properties and concentration, conditioned in several types of pharmaceutical formulations and for which information on the quantitative composition or even the authorisation procedure is available.

Personal contributions

A first personal contribution was the proposal and application of additional validation criteria for the IVRT methodology (Chapter 4). The demonstration of sensitivity, specificity and selectivity against the theoretical concentration of acyclovir in the semisolid matrix was accompanied by the study of the influence of quantitative composition variations applied to two distinct categories of excipients. The discriminatory nature of the methodology was verified by assessing the reference product, for which the presence or absence of three components leads to microstructural differences. The research identified and adequately characterized the two sources of non-similarity of *in vitro*

performances previously reported in the literature.

Another significant personal contribution is the application of the previously validated IVRT methodology in the comparative study of an extensive multisource product sample (Chapter 5). The inventory of available information on the qualitative composition was followed by the proposal of a dichotomous system and a grouping of components based on their structural and functional role, specific to the classification of TCS. The two approaches allowed the application of PCA procedures, through which the relationship between the Q1 similarity and the IVRT equivalence was demonstrated.

The research thesis proposes a new model of integration of Q1-Q2-Q3-IVRT relationships and correlations in the development and preparation of cream type experimental formulations containing 5% acyclovir (Chapter 6). The *in vitro* release methodology can detect, through sensitivity to microstructure differences, the influence of absorption promoters, although it uses a non-reactive interface, having reproducible characteristics and completely different from biological membranes.

Last but not least, the results obtained demonstrate the validity of the principles for the classification of topical drug products, confirm the central role of *in vitro* release tests and support the extension of the current application framework.

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