

Industrial approach to Rivaroxaban-Aspirin fixed-dose combination formulation

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Introduction

Emerging trends in pharmacological research are primarily centered around investigating drug-drug interactions, with the overarching objective of comprehensively elucidating the mechanisms and effects of interactions between different drugs (Niu et al. 2019, Strohhahn et al, 2021, Wang et al. 2021). Drug-drug interactions occur when two or more drugs are taken together, and their combined effects can differ from what would be expected if each drug were taken alone (Niu et al. 2019). Understanding these interactions is crucial for several reasons: (i) Enhanced Therapeutic Effects: Drug combinations can result in synergistic effects, where the combined effect of two drugs is greater than the sum of their individual effects; (ii) Drug Safety: On the other hand, drug-drug interactions can also lead to adverse effects; (iii) Pharmacokinetic Interactions: Drugs can interact at various stages of their absorption, distribution, metabolism, and elimination within the body.

One such compelling combination therapy gaining considerable attention is the formulation of Rivaroxaban and Aspirin within a single formulation (Eikelboom et al 2017). Rivaroxaban, an oral anticoagulant, acts by inhibiting the clotting factor Xa (Eikelboom et al., 2017, Papadaki & Tselepis, 2020), while Aspirin exerts its effects as an antiplatelet agent by inhibiting platelet aggregation (Patrono 1994). The combination of these two drugs has proven potential to achieve synergistic effects, resulting in enhanced anticoagulant and antiplatelet actions (Eikelboom et al., 2017). This combination therapy has shown promise in addressing the complex pathophysiology underlying arterial and venous thrombotic events, making it particularly relevant for patients at high risk, such as those with atrial fibrillation, deep vein thrombosis, or a

history of cardiovascular events (Eikelboom et al., 2017). By targeting distinct pathways involved in clot formation, this combination therapy aims to provide a broader spectrum of protection against both arterial and venous thromboembolic events. Beyond its therapeutic benefits, combining Rivaroxaban and Aspirin into a single formulation offers practical advantages as well. The simplified medication regimen provided by a single pill improves patient convenience and compliance. This streamlined approach enhances medication adherence, mitigates the risk of missed or incorrect doses, and ultimately contributes to improved treatment outcomes. Additionally, the combination therapy may allow for potential dose reduction, minimizing the adverse effects associated with higher individual drug doses. Formulating two drugs together is not a trivial task from the industrial point of view (Pourkavoos, 2012). Such an approach presents a unique set of challenges that demand careful consideration and scientific expertise. From a manufacturing perspective, the production of combination products entails its own set of complexities. Ensuring uniform distribution, consistent dosing, and maintaining stability throughout manufacturing processes require specialized techniques and equipment. The scalability of these manufacturing processes adds further complexity to the industrial implementation of combination drugs (Pourkavoos, 2012).

This scientific paper aims to provide a comprehensive overview of the challenges and considerations involved in formulating combination drugs, shedding light on the complexities faced by our company

Materials and methods

Granulates were manufactured on GEA HSWG systems: Collette MicroGral and Collette Gral 10.

Tablets were manufactured on tablet press Korsch XL100.

As granulation liquid, water dispersion of HPMC 3 mPas (Tylopor 603, ShinEtsu Pharma) with surfactant and purified water with surfactant were applied.

Dissolution studies were performed on Sotax AT7 USP II apparatus (paddle) with HPLC-DAD detection on Agilent 1100 system.

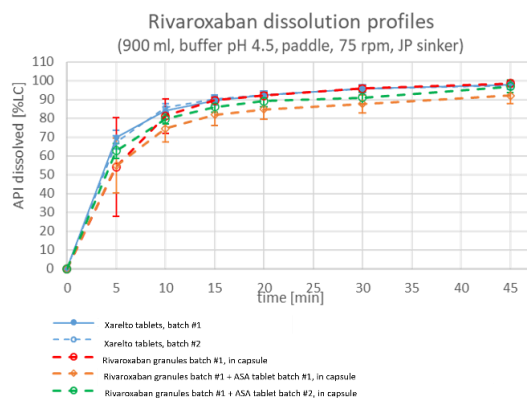


Figure 1. Rivaroxaban granules combined with ASA coated tablets – dissolution results.

Results and discussion

Among potential CQAs evaluated, the release rate of rivaroxaban was identified as a key critical attribute for product quality. Figure 1 illustrates the dissolution profiles of rivaroxaban granules combined with ASA tablets, providing a visual representation of the rivaroxaban release characteristics. The addition of tablets into the capsules has been observed to have a retarding effect on the dissolution of rivaroxaban, reflecting with slower release rate compared to the dissolution profiles of rivaroxaban alone.

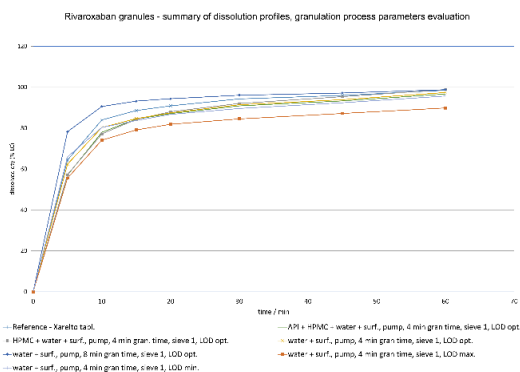


Figure 2. Rivaroxaban granules - summary of dissolution profiles, granulation process parameters evaluation.

To optimize the release profile of rivaroxaban, the following aspects were studied: 1) content of solids in granulation liquid; 2) granulation time; 3) dry sizing sieve size; 4) granulation liquid composition; 5) granulation liquid addition method, 6) moisture of dried granulate. All the factors were evaluated experimentally, allowing to obtain a robust, scalable granulation process providing acceptable similarity to the reference product dissolution profile, allowing to mitigate the impact of ASA tablet (Figure 2).

Conclusion

In conclusion, formulating two drugs together is a multifaceted task from an industrial standpoint, demanding expertise across various scientific disciplines. The challenges encompass chemical compatibility, physicochemical properties, and pharmacokinetics but as it can be observed the formulation method is also crucial from the practical point of view. By addressing these challenges head-on, pharmaceutical companies can unlock the potential of combination drugs to revolutionize therapeutic approaches and improve patient outcomes.

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