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Development of a biphasic *in vitro* dissolution test for the study of a BCS II API lipid-based oral dosage form produced by a PGSS process

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1. INTRODUCTION

The European Pharmacopeia (Eur. Ph.) describes four different testing apparatus for solid oral dosage forms and recommends to work under sink conditions. However, these conditions are not always discriminant or bio-relevant. The three main reasons are that the conventional media used in these tests have a little relevance to the *in vivo* situation, that phenomena of supersaturation or precipitation that can happen *in vivo* and that the solubility/permeability balance present *in vivo* are not taken into account. BCS class II Active Pharmaceutical Ingredients (API) present a good permeability but a poor oral bioavailability due to insufficient dissolution throughout the gastrointestinal tract. Maintaining sink conditions can be problematic for these compounds. To afford these conditions, several solubility modifiers should be added to dissolution media. However, the use of these additives is accompanied by inherent disadvantages. One emergent and attractive technique used to avoid solubility modifiers adding is the use of biphasic dissolution systems. This model is based on the fact that the presence of an upper organic phase within the aqueous dissolution medium could act as a reservoir for dissolved drug. In this way, the API, following initial aqueous dissolution, partitions into the organic layer, exploiting the lipophilicity of the compound.

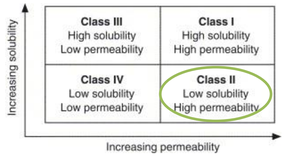

Fig. 1. Biopharmaceutics classification system (BCS)

2. MATERIALS AND METHODS

A biphasic dissolution test was compared with two single phase dissolution tests: one under sink conditions and another under non-sink conditions. This comparison was done for three different formulations of the same BCS II drug: pure API capsules, an improved bioavailability formulation available on the market and a PGSS lipid-based formulation with Gelucire® 50/13 (Gattefossé, France). For each test, three replicates were done and all samples were analyzed by a validated HPLC method.

Single phase dissolutions tests

A dissolution apparatus Eur.Ph. type IV (Fig.2) was used for both tests (sink and non-sink conditions). For the test under non-sink conditions the aqueous medium used was HCl 0,1 M. A surfactant (polysorbate 80) was added at the concentration of 1% to this medium for the test under sink conditions.

Fig. 2. Eur.Ph. apparatus type IV (Flow-through cell)

Biphasic dissolution tests

The biphasic dissolution system consisted of an aqueous phase (HCl 0,1 M) with an upper organic phase (octanol). The first test was performed in a slightly modified apparatus Eur.Ph. type II. A second paddle was added for the organic phase agitation.

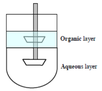

Fig. 3. Modified apparatus Eur. Ph. type II (Paddle apparatus) with a dual paddle

3. RESULTS AND DISCUSSION

Test under sink conditions

The pure API showed better drug release profile than the others formulations. However, for the market product, the bioavailability enhancement has been demonstrated in clinical studies. Therefore, this test seems to be discriminating but not bio-relevant.

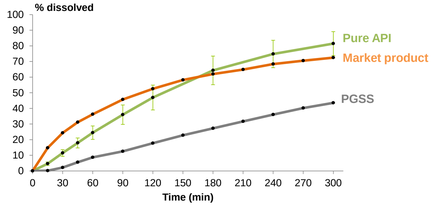

Fig. 4. Single phase dissolution test under sink conditions

Test under non-sink conditions

The test under non-sink conditions allowed to show an slight increase of the saturation concentration of API induced by the formulation with Gelucire® (PGSS in Fig.5). However, a complete API dissolution was never reached in these conditions. Thus it is difficult to accurately evaluate the rate of the drug release with this type of test.

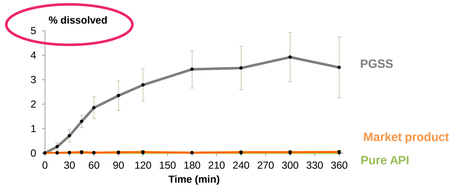

Fig. 5. Single phase dissolution under non-sink conditions

Biphasic test (with apparatus Eur. Ph. type II)

The first biphasic test was performed on the pure API capsules. As it can be seen in Fig.6, the concentration in the aqueous phase was almost undetectable while, the concentration in the organic phase increased quickly. In fact, due to their hydrophobic nature, the undissolved particles rise to the interface of the two phases and dissolve in the organic solvent. Therefore, the concentration in the organic phase was no longer dictated by the drug dissolved in the aqueous phase. This test was not relevant and we had to modify it.

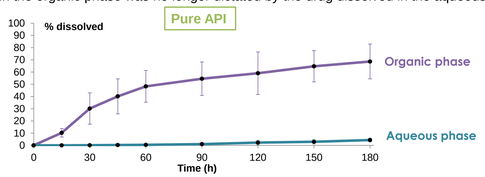

Fig. 6. Biphasic dissolution test on pure API (capsules) with apparatus Eur. Ph. Type II

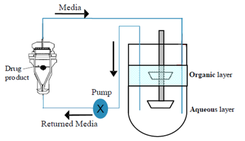

Fig. 7. Apparatus Eur. Ph. type IV combined to our modified apparatus Eur. Ph. type II

The modification that we did was to combine the apparatus Eur. Ph. type IV to our modified apparatus Eur. Ph. type II. In this way, the undissolved API particles remain trapped in the dissolution cell and can not rise to the organic phase.

Biphasic test (with apparatus Eur. Ph. type II combined to type IV)

For pure API, the concentration in the aqueous phase was always very low and corresponded to saturation concentration (C_S) in this medium. In the organic phase, the concentration was also very low but it increased continuously due to the transfer of dissolved API from aqueous phase.

The PGSS formulation showed higher API concentrations in the aqueous medium (C_{max}) as compared to the C_S found in the same medium after a saturation step with octanol. This suggests that a supersaturation of API due to the type of formulation can be detected by this dissolution test thanks to the presence of the organic phase.

The market product showed similar API concentrations in the aqueous medium as compared those observed in the single phase dissolution test under non-sink conditions (= C_S). This suggests that this formulation does not allow the establishment of a supersaturation during dissolution. However, it allows a faster transfer of dissolved API from aqueous phase to organic phase compared to pure API.

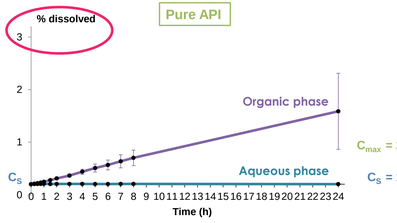

Fig. 8. Biphasic dissolution test on pure API (capsules) with apparatus Eur. Ph. Type II combined to type IV

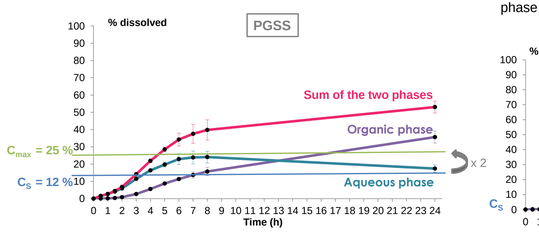

Fig. 9. Biphasic dissolution test on PGSS production with apparatus Eur. Ph. Type II combined to type IV

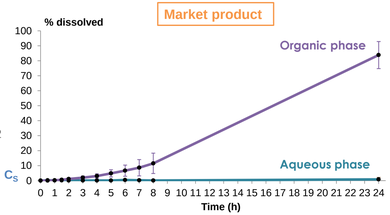

Fig. 10. Biphasic dissolution test on market product with apparatus Eur. Ph. Type II combined to type IV.

4. CONCLUSIONS

Given these results, we can conclude that the test under sink conditions seems to be a poor bio-relevant test. In the test under non-sink conditions, the medium is rapidly saturated limiting the dissolution process. And finally, a complete dissolution of the API is possible in a biphasic test due to the continuous extraction of the dissolved drug from the aqueous phase into the organic phase. Furthermore, the biphasic *in vitro* test method appears to be a useful tool for the performance evaluation of formulations containing poorly water-soluble drugs, especially if they lead to *in vivo* supersaturation. Considering that this test takes into account the dissolution and the partition step, *in vitro-in vivo* correlation could be easier to establish.

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