

# Letter to the Editor

## Comment on: Comparative dissolution profiles of two anti-emetic delayed-release dosage forms of doxylamine and pyridoxine: Xonvea<sup>®</sup> tablets vs. Cariban<sup>®</sup> capsules

Dear Editor,

We have read the article by Alcocer et al<sup>1</sup> with great interest; it presents a comparative study of two anti-emetic doxylamine/pyridoxine formulations. Therein we detected a series of inaccuracies, as well as some reported data that could be considered to be misleading; this fact calls into question the precision of the conclusions. The present paper provides additional *de novo* data and information from the literature, all of which refutes some of the claims made by the aforementioned authors.

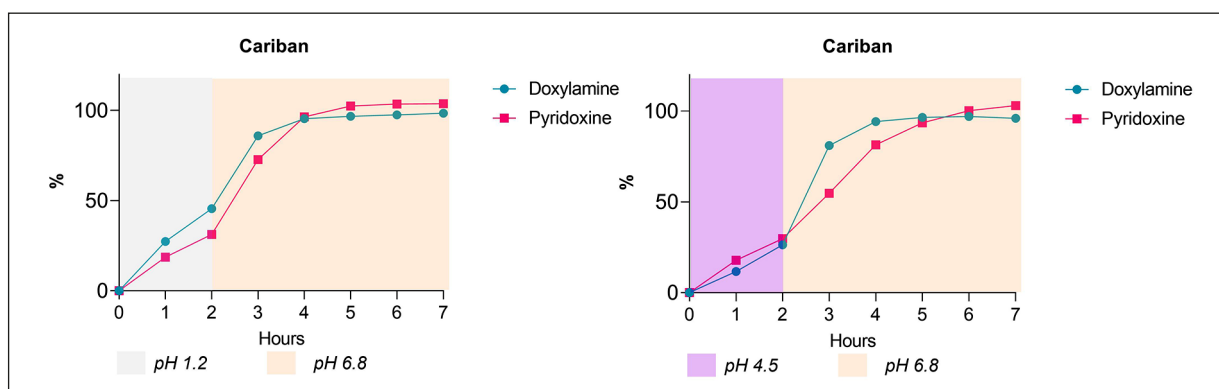
Modified-release formulations encompass different types of release performances<sup>2</sup>. Herein, Cariban<sup>®</sup> is wrongly defined as “delayed-release”<sup>1</sup>; in reality, it is an extended-release formulation that releases its content over 6-7 hours, in accordance with expected gastrointestinal transit time<sup>3</sup>, and starting at the stomach level. To show the complete performance of the Cariban<sup>®</sup> formulation *in vitro*, we performed a dissolution profile, under the same conditions indicated in Alcocer et al<sup>1</sup> but prolonged up to 7 hours.

In Figure 1 two dissolution conditions are shown; for both, the total duration of the assay is 7 hours. The dissolution was performed in two steps, 2 hours in acidic pH (in HCl 0.1N pH 1.2 or in acetate buffer pH 4.5) and 5 hours in phosphate buffer at pH 6.8. The dissolution test was performed in an Agilent 708-DS apparatus, under the following conditions (Table I). For each *in vitro* dissolution test, 6 hard-gelatin capsules (Navalit<sup>®</sup>/Cariban<sup>®</sup>; Lot No. T24 exp. 03/2024) were used. Samples from dissolved capsules at each timepoint were collected and doxylamine and pyridoxine release was measured by RP-HPLC/DAD (Reverse Phase High-Performance Liquid Chromatography-Photodiode Array Detector). We calculated the percentage of dissolved active substances by means of the concentration of the volume sampled at each time and using the theoretical content of actives per capsule as 100%.

Figure 1 shows that doxylamine and pyridoxine are fully released after 5-7 hours, depending on initial pH conditions. After 2 hours at pH 1.2 and pH 4.5, which mimic gastric digestion conditions, pyridoxine is released at approximately 32% and 31%, respectively, while doxylamine is released at 45% and 26%, respectively. After coming into contact with a pH 6.8 buffer, both active substances continue to discharge, reaching a dissolution rate of over 95% after 5 hours.

Comparing their behavior *in vitro*, Alcocer et al<sup>1</sup> conclude that Xonvea<sup>®</sup> shows no release in acidic pH, protecting from degradation, while Cariban<sup>®</sup> does<sup>1</sup>. The stability of doxylamine/pyridoxine in acidic pH has been well established and reported<sup>4-7</sup> and no degradation is observed in the Cariban<sup>®</sup> dissolution profile, in which 100% of the actives are recovered (Figure 1).

Additionally, the authors claim that Cariban<sup>®</sup> does not reach complete dissolution, while Xonvea<sup>®</sup> does<sup>1</sup>. Considering that Cariban<sup>®</sup> is a modified-release formulation<sup>8,9</sup>, a 3-hour dissolution testing is insufficient with regard to observing the full dissolution of the active ingredients, which is expected to occur after 7 hours (Figure 1).



**Figure 1.** Seven-hour *in vitro* dissolution profile of doxylamine (blue line) and pyridoxine (pink line) from Cariban®/Navalit® capsules. Percentage of actives dissolved over time is shown. Methods as in Alcocer et al<sup>1</sup>, with the only difference of 5 hours at pH 6.8 instead of 1h.

**Table I.** Conditions of the dissolution test performed in an Agilent 708-DS apparatus.

Average temperature	37 ± 0.5°C
Volume	900 ml
Apparatus	Paddles (USP type II)
Rotation speed	50 rpm
Sampling volume	5

Furthermore, it is scientifically inappropriate to interpret *in vitro* data referring to modified-release formulations as the dynamics of drug absorption, the onset of action or the therapeutic effects (e.g. “*This could translate into faster onset of action and relief of nausea for pregnant women taking the tablets vs. the capsules*”); this should be demonstrated clinically<sup>2</sup>; inferred conclusions go somewhat beyond speculation.

In Table III of their article, the authors selectively present results of distinct pharmacokinetic studies<sup>1</sup>. While the data referring to Xonvea® report doxylamine values as a single unit, the comparative data referring to Cariban® are reported separately, in relation to the two doxylamine enantiomers, thus giving the misleading impression that the values provided by the tablets are greater than the capsules. Surprisingly, other relevant pyridoxine active metabolites, such as pyridoxal 5-phosphate<sup>10</sup> are absent. Whatever the case, it is deemed to be scientifically inappropriate to arbitrarily compare different studies, involving different subjects and methodologies and lacking the required controls. Consequently, the conclusions of the article are insufficiently supported by this comparison.

In our opinion, this study by Alcocer et al<sup>1</sup> involves a whole series of issues of ethical concern; this would invalidate their conclusions, and these can lead readers to a misunderstanding.

### Conflict of Interest

All the authors are employees of the Italfarmaco Group.

### References

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