

Comparative dissolution profiles of two anti-emetic delayed release dosage forms of doxylamine and pyridoxine: Xonvea® tablets vs. Cariban® capsules

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Abstract. – OBJECTIVE: Nausea and vomiting of pregnancy is a common disease that affects many women suffering from mild to severe symptoms. Amongst the different treatments, a fixed dose combination of doxylamine and pyridoxine has been proven safe and effective although the mechanism of action is not well established. There are different pharmaceutical dosage forms in the European market. The objective of this study was to compare the characteristics of a capsule formulation, Cariban® and a tablet formulation, Xonvea® to evaluate the potential impact of their release profiles on their onset of action.

MATERIALS AND METHODS: 10 mg/10 mg of doxylamine succinate/pyridoxine hydrochloride capsules (Cariban®) and tablets (Xonvea®) were used as reference materials. Appearance, mass, composition, and *in vitro* dissolution profiles were compared. Bibliographic data from 4 pharmacokinetic studies of Xonvea® and 1 pharmacokinetic study of Cariban® was reviewed.

RESULTS: *In vitro* dissolution studies showed significant differences in dissolution profiles of tablets and capsules. The later exhibiting some release of both drug substances in acid conditions followed by a non-complete release after a total of 3 hours while the tablets demonstrated gastro-resistant properties and rapid API release in about 20-30 minutes after the acid stage. Comparison of PK data showed greater C_{max} for pyridoxine.

CONCLUSIONS: At pH 6.8, complete and faster release of the fixed dose combination for Xonvea® gastro-resistant tablets compared to Cariban® capsules could possibly explain the greater C_{max} observed *in vivo* for the tablet's formulation. This could translate into faster onset of action and relief of nausea for pregnant women taking the tablets vs. the capsules.

Key Words:

Nausea, vomiting, Pregnancy, Doxylamine, Pyridoxine, Dissolution profile, Performance, Pharmaceutical quality.

Introduction

Nausea and vomiting of pregnancy (NVP) are a common condition that affects about 70% of pregnant women worldwide¹. Symptoms vary from mild nausea to severe form of NVP, which is called hyperemesis gravidarum (HG) with excessive vomiting, dehydration, electrolyte imbalances, and weight loss². HG occurs in 1.1% of all pregnancies¹ and, in the United States, hyperemesis gravidarum is the most common cause of hospitalization during the first half of pregnancy and is second only to preterm labour for hospitalizations in pregnancy overall². NVP decreases the quality of life and has major economic influence often causing absence from work³. These are USA data that can differ from other parts of the world.

The anti-emetic combination of vitamin B6 (pyridoxine) and the antihistamine doxylamine is the most extensively studied NVP medication regarding safety in pregnancy⁴. This combination has been highlighted as a first line pharmacologic treatment for NVP in US⁴, Canada⁵ and Ireland clinical guidelines of the Institute of Obstetricians and Gynaecologists⁶. Since the etiology of NVP is not well-known, despite the proven efficacy of the fixed dose combination of doxylamine and pyridoxine in the treatment of NVP its mechanism of action is not well established.

The delayed-release, fixed dose combination of doxylamine succinate and pyridoxine hydrochloride, as a treatment for nausea and vomiting of pregnancy was first introduced to the market by Merrell Dow in 1958 as Debendox® (Merrell Dow, NY, USA), but within a triple active combination containing 10 mg of each of doxylamine succinate, pyridoxine hydrochloride and dicyclomine hydrochloride. The product was reformulated in 1976 and dicyclomine hydrochloride was removed as it was found not to contribute to the anti-emetic properties of the drug combination⁷. The reformulated product was available as Debendox® in the UK and Australia, Lenotan® in Germany, Merbental® in Spain and Bendectin® in North America. In 1983, Merrell Dow voluntarily withdrew the product from the market due to excessive costs of defending non-meritorious lawsuits alleging teratogenicity. Numerous epidemiological studies⁸⁻¹⁰, performed because of this litigation, have demonstrated that pyridoxine/doxylamine does not affect the incidence of congenital anomalies. Over the last decades many studies and two meta-analyses have confirmed the fetal safety of this drug combination^{8,11}. The US Food and Drug Administration and the UK Committee on Safety of Medicines have both noted that the product was not withdrawn from sale for reasons of safety or effectiveness^{12,13}.

A Canadian parliamentary assessment of the safety of pyridoxine/doxylamine in the 1980s led to the Canadian product Diclectin® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed release tablets – Duchesnay Inc., Blainville, QC, Canada) remaining on the market¹⁴. In 2013, the same product was also approved in the USA, under Diclegis® name¹⁵, following a randomized placebo-controlled trial which showed it was effective and well tolerated¹⁶.

Since 2018, the same delayed release tablets formulation is also available in different European countries under Xonvea® 10 mg/10 mg gastro-resistant tablets name by MHRA¹⁷. The product has been first approved in the UK in 2018 considering the Koren et al¹⁶ study together with another randomized placebo-controlled trial in 14 US centers undertaken in 1975⁷. After that, it has also been recently approved in other European countries through Decentralized Procedure¹⁸. Complementary data on the study by Koren et al¹⁶ is reported on several publications¹⁹⁻²¹.

In parallel to the delayed release tablet formulations, a Spanish company developed and

marketed a modified release hard capsule formulation comprising the same fixed dose combination of pyridoxine HCl 10 mg and doxylamine succinate 10 mg (Cariban®, Laboratorios Inibsa, S.A.). Cariban® 10 mg/10 mg modified release hard capsules were first approved in Spain in 1967 and later in 2017 was granted with an extension to other European countries through a Decentralized Procedure (Navalem®, Nuperal®, Navalit®)²². To the best of our knowledge, there are no randomized placebo-controlled trials published with Cariban® 10 mg/10 mg modified release hard capsules.

These two pyridoxine/doxylamine fixed dose combination products are described with some slight differences in their release characteristics, but both share the same functional polymer [methacrylic acid-ethyl acrylate copolymer (1:1)] and can be considered as delayed release formulations. Cariban® entitled as modified release hard capsules product has its active substances incorporated into coated microgranules with a dialyzing membrane that completely releases the active substances after a certain period (Inibsa Ginecología S.A., 2022). Therefore, both active substances have a delayed onset of action. This product is composed of two types of modified-release pellets, one for each active ingredient. Those pellets are filled together in hard gelatin capsules²³. Meanwhile, Xonvea® 10 mg/10 mg gastro-resistant tablets are formulated with both active substances in the tablet core and an enteric coating to protect the tablet until it has passed through the stomach. After this period, both active substances quickly reach the onset pharmaceutical effect; once inside the intestine, the product is formulated to immediately release both active ingredients, and both are absorbed^{15,24}.

As a result, for the dosing schedule of both drug formulations it is important to ensure that the onset of action occurs when NVP symptoms are at their peak taking into consideration the delayed absorption once the drugs reach the intestine. The standard recommended dose of Cariban® (Inibsa Ginecología S.A., 2022) and Xonvea® (Exeltis Healthcare S.L., 2021²⁵) is typically 40 mg pyridoxine/doxylamine (four tablets) a day: 20 mg at bedtime, 10 mg in the morning, and 10 mg in mid-afternoon, because NVP symptoms are thought to be worst in the morning¹⁴. However, it is important to adjust the schedule according to the pattern of NVP in a particular individual. Higher-than-standard doses of pyridoxine/doxylamine have been studied in pregnancy with some

women requiring up to 120 mg (12 tablets) a day with no apparent increased of maternal or fetal risks²⁶.

The aim of this study is to evaluate the *in vitro* behavior differences between the two different pyridoxine/doxylamine fixed dose formulations available in the European market – Cariban[®] 10 mg/10 mg modified release hard capsules and Xonvea[®] 10 mg/10 mg gastro-resistant tablets.

To better characterize the possible differences between both formulations, a bibliographical review of available pharmacokinetics data has been performed.

Bibliographical Review of Pharmacokinetic Studies

Both formulations are designed to achieve the absorption of their active ingredients in the gastrointestinal (GI) tract, mainly in the jejunum²⁷. Pyridoxine is absorbed in the jejunum of the small intestine by passive diffusion^{28,29}. Doxylamine is metabolized by the liver to N-desmethyldoxylamine and N, N-didesmethyldoxylamine. These two metabolites are excreted by the kidney. Pyridoxine is a prodrug that is primarily metabolized in the liver to 5 active metabolites³⁰.

Poor information is available regarding the pharmacokinetics of the pyridoxine/doxylamine modified release hard capsules formulation. One study examined the pharmacokinetic effects of doxylamine in 12 healthy women volunteers receiving an oral dose of 2 capsules (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) in fasted and fed state. The mean pharmacokinetics parameters (\pm SD) for R-doxylamine, S-doxylamine, pyridoxine and pyridoxal under fasting conditions are presented in Table I (Inibsa Ginecología S.A., 2022).

The onset of pyridoxine/doxylamine modified release hard capsules pharmacological effects is delayed and C_{max} is reached at approximately 6-7 hours after ingestion in fasted conditions for doxylamine and at approximately 4 hours for pyridoxine (Inibsa Ginecología S.A., 2022).

Instead, much more information can be found in the public domain for pyridoxine/doxylamine

gastro-resistant tablets formulation. Pharmacokinetics of this medicinal product has also been found in healthy non-pregnant adult women.

Four pharmacokinetic studies^{17,18}, under fasting conditions, of pyridoxine/doxylamine gastro-resistant tablets have been included in this review. In all studies the administered dose was 2 × 10 mg/10 mg gastro-resistant tablets:

Food Effect Study - 70294 (MHRA 2018; HPRA 2021)

A randomized, open-label, 2-way crossover relative bioavailability study of Doxylamine/Pyridoxine 10 mg/10 mg (Diclectin[®] delayed-release tablets) following a 2 × 10 mg/10 mg dose in 44 healthy adult females under fasting and fed conditions.

Pivotal Study - 160286 (MHRA 2018; HPRA 2021)

A randomized, open-label, 3-way crossover comparative bioavailability study comparing Diclectin[®] 10 mg/10 mg delayed-release tablets (A) with Doxylamine 20 mg delayed-release tablet (B) and Pyridoxine 20 mg delayed-release tablet (C), following a single dose of 20 mg Doxylamine and/or 20 mg Pyridoxine in healthy subjects under fasting conditions.

Supplementary Bioequivalence Study - 02163 (MHRA 2018; HPRA 2021)

A randomized, single dose, open-label, 2-way, crossover relative bioavailability study to compare the rate and extent of absorption of Diclectin[®] vs. a combination of doxylamine succinate 10 mg/10 mL and pyridoxine hydrochloride 10 mg/10 mL oral solutions administered as 2 × 10 mg/10 mg delayed-release Tablets or 1 × 20 mL + 1 × 20 mL oral solutions under fasting conditions in healthy subjects.

Relative Bioavailability Study - 70381 (MHRA 2018; HPRA 2021)

A single and multiple-dose (40 mg/day), open-label, 1-way study to assess the pharmacokinetic profile and safety of Diclectin[®] delayed-release tablets healthy, non-pregnant female subjects, administered under fasting conditions.

Pharmacokinetic results from the gastro-resistant tablets formulation and the modified release hard capsules for doxylamine and pyridoxine, including the vitamin B6 metabolite pyridoxal are summarized in Table I and reviewed in the discussion section.

Table I. Dissolution test conditions.

Temperature	37 ± 0.5°C
Volume	1,000 mL
Apparatus	Paddles (USP type II)
Speed	50 rpm
Sampling volume	5 mL

Materials and Methods

Analyses were performed according to the standard physical and chemical laboratory tests developed and routinely practiced at Laboratorios Liconsa S.A. facilities (Azuqueca de Henares, Spain).

Samples of Xonvea® tablets (Lot No. 1564V-1 exp. 08/2024) and Cariban® capsules (Lot No. S11 exp. 09.2023) were purchased in the year 2021 in pharmacies, kept in laboratory environmental conditions and analyzed within their expiry dates.

Mass of Samples

10 tablets were weighed, and average mass was calculated. 10 capsules were weighed, emptied and the emptied capsules were weighed; content weight was determined by the difference between filled capsule and shell weights.

In Vitro Dissolution Test

Xonvea® 10 mg/10 mg gastro-resistant tablets and Cariban® 10 mg/10 mg modified release hard capsules were tested *in vitro* to study if these *in vivo* differences can be found between both products. Table I depicts the dissolution test conditions.

Two different dissolution conditions were evaluated: pH 1.2 (2 hours), followed by phosphate buffer pH 6.8, and acetate buffer pH 4.5 (2 hours), followed by phosphate buffer pH 6.8. Dissolution apparatus brand is Agilent 708-D. Samples were collected and analyzed according to a RP-HPLC/DAD method routinely used in the laboratory.

Results

Characteristics and Composition of Pharmaceutical Dosage Forms

Tablets and capsules were of similar total weight with the same functional polymer [Methacrylic acid-methyl acrylate copolymer (1:1)] within their composition (Table II).

The active pharmaceutical ingredients of both compounds are 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride.

The excipient composition of Xonvea® is composed of:

- Tablet Core: Microcrystalline cellulose, magnesium trisilicate, croscarmellose sodium, magnesium stearate and colloidal anhydrous silica.

- Coating: Hypromellose, macrogol 400 and 8,000, methacrylic acid-ethyl acrylate copolymer (1:1), talc, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, triethyl citrate, simeticone emulsion, titanium dioxide, polysorbate 80, waxing, carnauba wax, printing ink, shellac, allura red AC aluminum lake, propylene glycol, indigo carmine aluminum lake and simeticone emulsion.

The excipient composition of Cariban® is composed of:

- Content: Saccharose (79.5 mg), starch maize, shellac, povidone, talc, methacrylic acid-methyl acrylate copolymer (1:1) and colloidal anhydrous silica,
- Capsule Shell: Gelatin, indigo carmin, yellow quinolein, titanium dioxide.



The different techniques used and the differences in the pharmacological forms of pyridoxine/doxylamine fixed-dose combinations seem to have an essential role concerning the behavior of capsules vs. tablets (Table II).

Dissolution Testing

Characterization of the dissolution of both products was performed under two different condition media. The selected media were based on the onset pharmaceutical effect of both compounds when formulated (in capsules or tablets). Those media were considered predictive and intended to mimic *in vivo* performance conditions along the gastrointestinal tract once tablets or capsules are taken³¹.

Capsules and tablets showed significant release profiles for both doxylamine and pyridoxine according to the different test conditions. After 2 hours at pH 1.2 and pH 4.5, drug substances from Cariban® modified release hard capsules are releasing about 23% and 20% in the case of Doxylamine respectively and 35% and 26% of Pyridoxine respectively. However, Xonvea® gastro-resistant tablets do not show any release of drug substances after this period (pH 1.2 or pH 4.5), protecting them from any degradation due to acidic pH. Once the drug product gets in contact with pH 6.8 (phosphate buffer), after a small lag of around 5 minutes, Xonvea® quickly releases the drugs, reaching more than 90% dissolution of both products within 20 minutes. In contrast, Cariban®, in the equivalent length of time (20 minutes), released only around 5% of doxylamine and 10% of Pyridoxine accounting for less than

Table II. Characteristics of Xonvea® tablets and Cariban® capsules (composition from Exeltis Healthcare S.L. 2021 and Inibsa Ginecología S.A. 2022, respectively).

Characteristics	Xonvea®	Cariban®
Pictures		
Description	Round biconvex film coated tablets.	Size #3 capsule with granular content
Dimensions	8.22 mm (diameter) × 3.27 mm (thickness).	15.53 mm (height) × 5.77 mm (diameter)
Weight	167.67 mg (0.9% RSD).	Total: 168.21 mg (3.2% RSD) Content: 120.46 mg (3.4% RSD)
Excipient composition	Tablet core Microcrystalline cellulose Magnesium trisilicate Croscarmellose sodium Magnesium stearate Colloidal anhydrous silica Coating Hypromellose Macrogol 400 and 8000 Methacrylic acid-ethyl acrylate copolymer (1:1) Talc Colloidal anhydrous silica Sodium bicarbonate Sodium lauryl sulphate Triethyl citrate Simeticone emulsion Titanium dioxide Polysorbate 80 Waxing Carnauba wax Printing ink Shellac Allura Red AC aluminum lake Propylene glycol Indigo carmine aluminum lake Simeticone emulsion	Content Saccharose (79.5 mg) Starch maize Shellac Povidone Talc Methacrylic acid-methyl acrylate copolymer (1:1) Colloidal anhydrous silica Capsule shell Gelatin Indigo carmin Yellow quinolein Titanium dioxide

40% drug dissolution. By 180 minutes, Cariban® had not reached complete dissolution of any of the drug substances. The Figures 1-4 depict the different results.

It can be clearly seen that at pH 4.5 there is no dissolution for Doxylamine and Pyridoxin after 120 minutes for Xonvea®, whereas for Cariban® a dissolution of 20% for Doxylamine and 17% for Pyridoxine is observed. After only 20 minutes, an almost 100% dissolution is observed for Doxylamine at the pH of 6.8 for Xonvea® whereas for Cariban® a dissolution rate of only 46% after 60 minutes is observed.

Similar results were seen for Pyridoxine. Dissolution rates of 0% up to 120 minutes in a pH of 4.5 and of up to 92% after 20 minutes in a pH of 6.8. In comparison the values for Cariban® were

28% at 120 minutes at a pH of 4.5 and 65% 60 minutes later at a pH of 6.8.

Table III shows that Xonvea® seems to give a higher peak of absorption (C_{max}) compared to Cariban® for Pyridoxine and its metabolite Pyridoxal. Extent of absorption (AUC) cannot be evaluated since data for Cariban® is not available in the public domain.

The C_{max} (ng/mL) of Doxylamine in Xonvea® was between 83.26±20.62 and 95.77±15.46, whereas the C_{max} (ng/mL) in Cariban® was 43.78±5.64 for the s form and 47.30±6.25 for the r form. The following values were obtained for Pyridoxal: Xonvea® between 62.3±19.1 and 85.39±21.53, whereas the C_{max} (ng/mL) in Cariban® was 35.85±9.51.

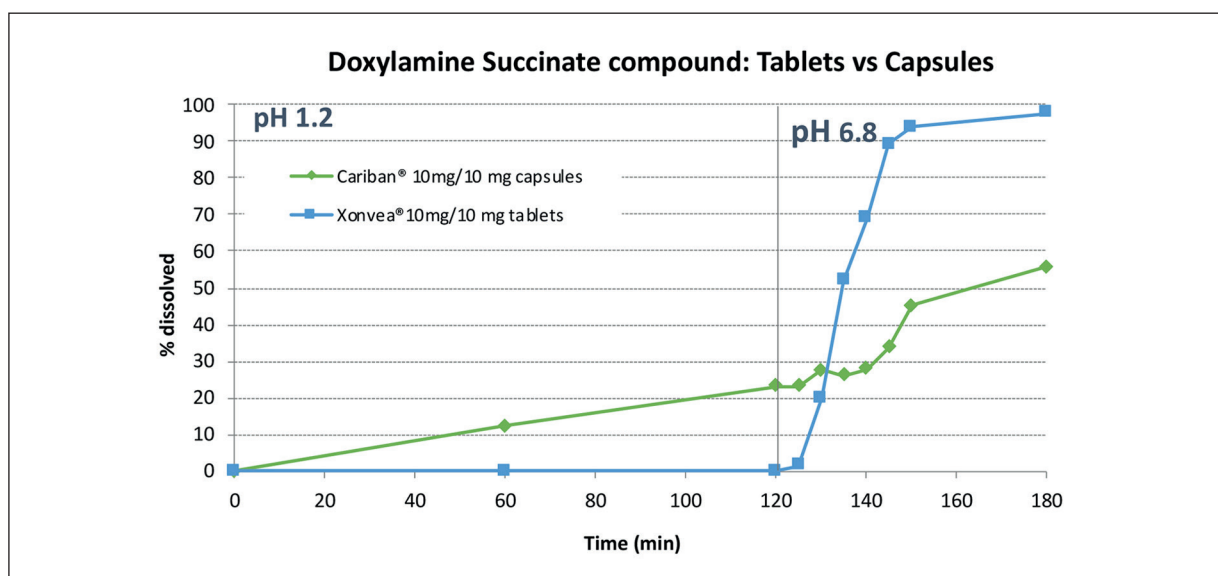


Figure 1. Comparison of dissolution profile between tablets and capsules: pH 1.2 + phosphate pH 6.8. Dissolution profile comparison for Doxylamine Succinate compound: Tablets (Xonvea® 10 mg/10 mg gastro-resistant tablets, square symbols, and blue line) vs. Capsules (Cariban® 10 mg/10 mg modified release hard capsules, diamond symbols and green line): USP II (paddles), 50 rpm: pH 1.2 (2 hours) + pH 6.8 phosphate buffer.

The Tmax (h) of Doxylamine in Xonvea® was between 4.50 (1.50-24.0) and 7.50 (3.33-11.00), whereas the Tmax (h) in Cariban® was 6.50±1.37 for the s form and 6.58±1.52 for the r form.

The Tmax (h) of Pyridoxal was between 3.03 (1.02-5.00) and 6.00 (3.33-9.00) for Xonvea® and 4.94±1.04 for Cariban®.

Discussion

According to their composition, Xonvea® tablets seems to be manufactured by direct compression technology (dry powder blend) to get uncoated tablets, named as cores as well. After that, those cores are coated by a coating process

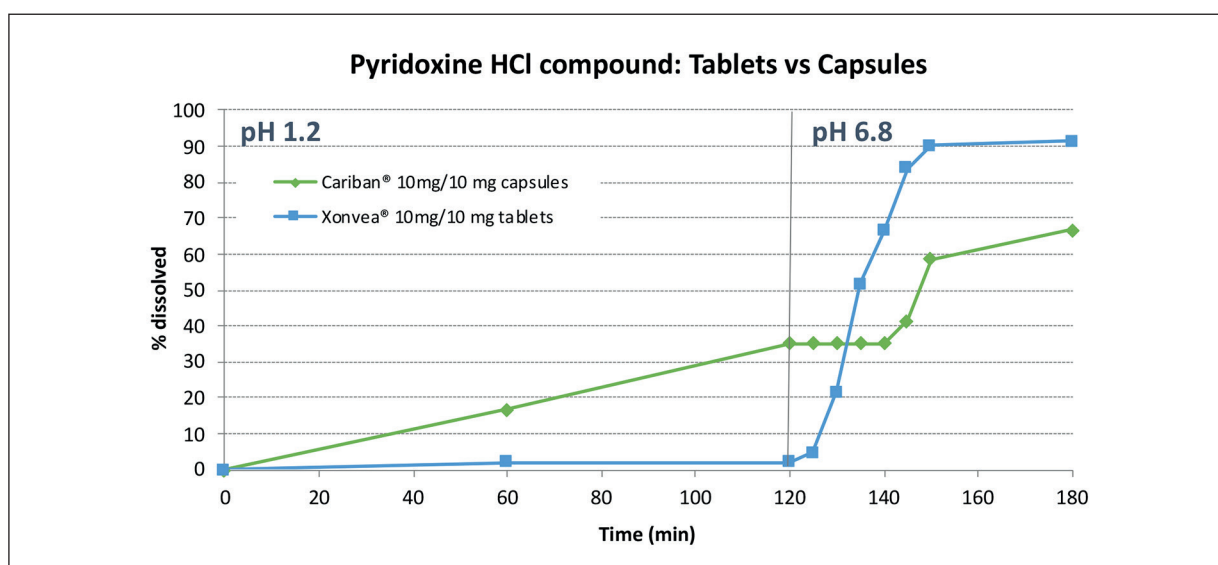


Figure 2. Dissolution profile comparison for Pyridoxine HCl compound: Tablets (Xonvea® 10 mg/10 mg gastro-resistant tablets, square symbols, and blue line) vs. Capsules (Cariban® 10 mg/10 mg modified release hard capsules, diamond symbols and green line): USP II (paddles), 50 rpm: pH 1.2 (2 hours) + pH 6.8 phosphate buffer.

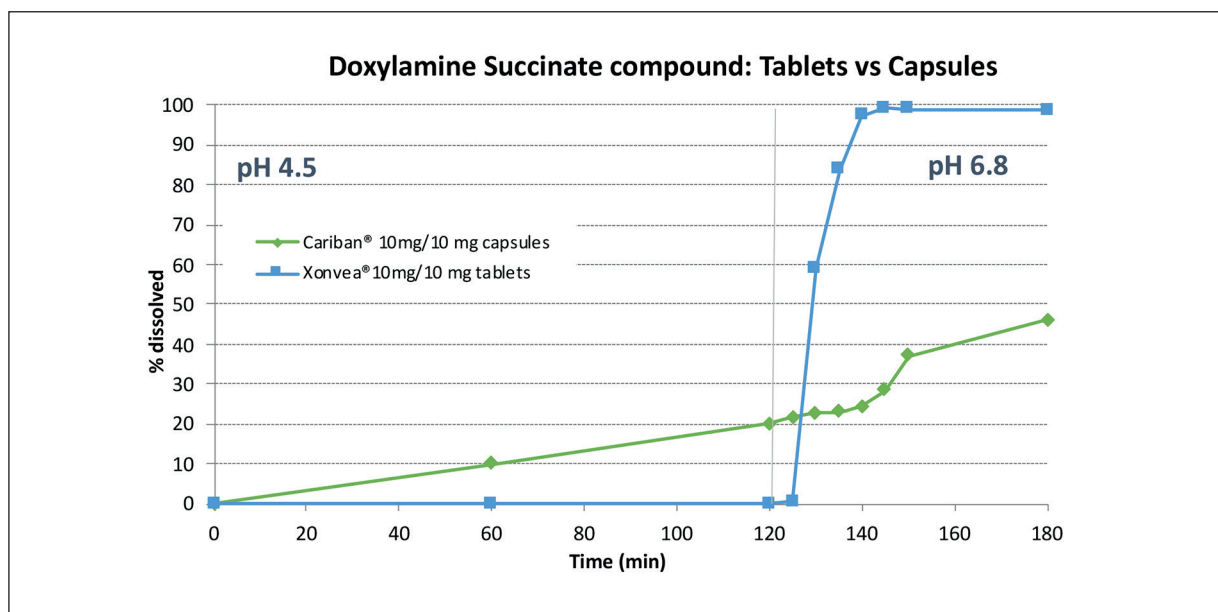


Figure 3. Comparison dissolution profile between tablets vs. capsules: acetate pH 4.5 + phosphate pH 6.8. Dissolution profile comparison for Doxylamine Succinate compound: Tablets (Xonvea® 10 mg/10 mg gastro-resistant tablets, square symbols, and blue line) vs. Capsules (Cariban® 10 mg/10 mg modified release hard capsules, diamond symbols and green line): USP II (paddles), 50 rpm: pH 4.5 acetate buffer (2 hours) + pH 6.8 phosphate buffer.

with the functional polymer [Methacrylic acid-ethyl acrylate copolymer (1:1)] conferring its gastro-resistant characteristics (Figure 5). After tablet intake, when pH increases after gastric emptying, this functional polymer starts to break down releasing the complete amount of both drug substances.

On the other hand, Cariban® capsules are composed by two different population of pellets (or microgranules) (Figure 6) and seems to be made by layering process technology. Once these two types of pellets or microgranules are obtained, they are then encapsulated, and they become capsules (Figure 7).

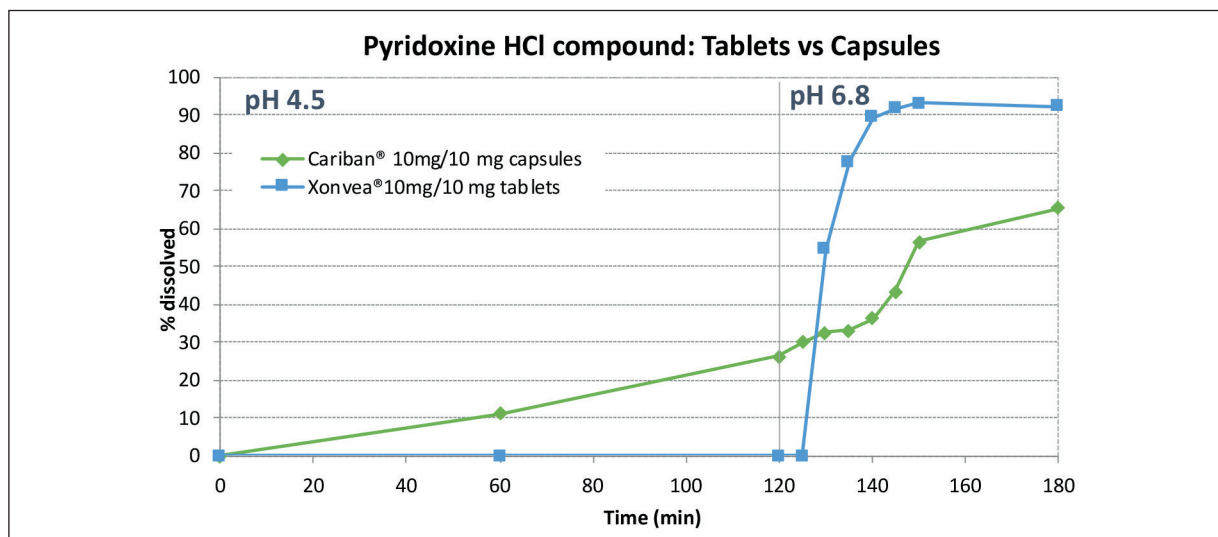


Figure 4. Dissolution profile comparison for Pyridoxine HCl compound: Tablets (Xonvea® 10 mg/10 mg gastro-resistant tablets, square symbols, and blue line) vs. Capsules (Cariban® 10 mg/10 mg modified release hard capsules, diamond symbols and green line): USP II (paddles), 50 rpm: pH 4.5 acetate buffer (2 hours) + pH 6.8 phosphate buffer.

Anti-emetic delayed release: Xonvea® tablets vs. Cariban® capsules

Table III. Comparison of mean pharmacokinetics parameters (± SD) of Xonvea® gastro-resistant tablets and Cariban® modified release hard capsules under fasted conditions in healthy volunteers.

Analyte	Doxylamine						Pyridoxine					Pyridoxal				
	Xonvea®				Cariban®		Xonvea®				Cariban®	Xonvea®				Cariban®
	70294	160286	02163	70381	NA	NA	70294	160286	02163	70381	NA	70294	160286	02163	70381	NA
Study Code				R-doxylamine	S-doxylamine											
AUC _{last} (ng·h/mL)	1407.20 ± 336.94	1385.57 ± 392.53	NA	911.40 ± 205.62	NA	NA	33.75 ± 13.71	44.37 ± 12.88	NA	39.34 ± 6.53	NA	193.66 ± 53.95	NA	NA	187.46 ± 44.69	NA
AUC _{0-72h} (ng·h/mL)	NA	NA	NA	NA	NA	NA	NA	N/A	NA	NA	NA	NA	NA	NA	NA	NA
AUC _{0-24h} (ng·h/mL)	NA	NA	NA	911.40 ± 205.62	NA	NA	NA	NA	NA	40.70 ± 16.45	NA	NA	NA	NA	195.13 ± 46.18	NA
AUC _{inf} (ng·h/mL)	1447.89 ± 332.18	1446.31 ± 443.76	NA	1280.90 ± 369.32	NA	NA	39.48 ± 12.85	44.67 ± 12.94	NA	43.39 ± 16.46	NA	231.20 ± 71.75	NA	NA	211.60 ± 46.09	NA
C _{max} (ng/mL)	94.90 ± 18.40	95.77 ± 15.46	90.4 ± 13.1	83.26 ± 20.62	47.30 ± 6.25	43.78 ± 5.64	35.54 ± 21.40	50.33 ± 24.13	50.7 ± 31.0	32.57 ± 15.03	15.80 ± 2.96	85.39 ± 21.53	NA	62.3 ± 19.1	74.29 ± 21.80	35.85 ± 9.51
T _{max} (h)	4.50 (1.50 - 24.0) *	5.00 (3.00-5.50) *	6.00 (3.00 – 10.00) *	7.50 (3.33-11.00) *	6.58 ± 1.52	6.50 ± 1.37	2.50 (1.00 - 4.52)	2.50 (1.00-4.67)	4.00 (1.50 – 5.50)	5.50 (2.67-9.02)	3.89 ± 0.98	3.03 (1.02 - 5.00)	NA	5.00 (2.33 – 8.00)	6.00 (3.33-9.00)	4.94 ± 1.04
t _{1/2} (h)	12.64 ± 3.43	12.13 ± 2.32		10.05 ± 2.09	10.84 ± 2.65	12.33 ± 2.02	0.37 ± 0.16	0.60 ± 1.00		0.49 ± 0.23	1.90 ± 1.38	2.14 ± 2.18	NA	NA	1.29 ± 0.50	118.56 ± 51.88

Reproduced from MHRA 2018; Inbsa Ginecología S.A. 2022.

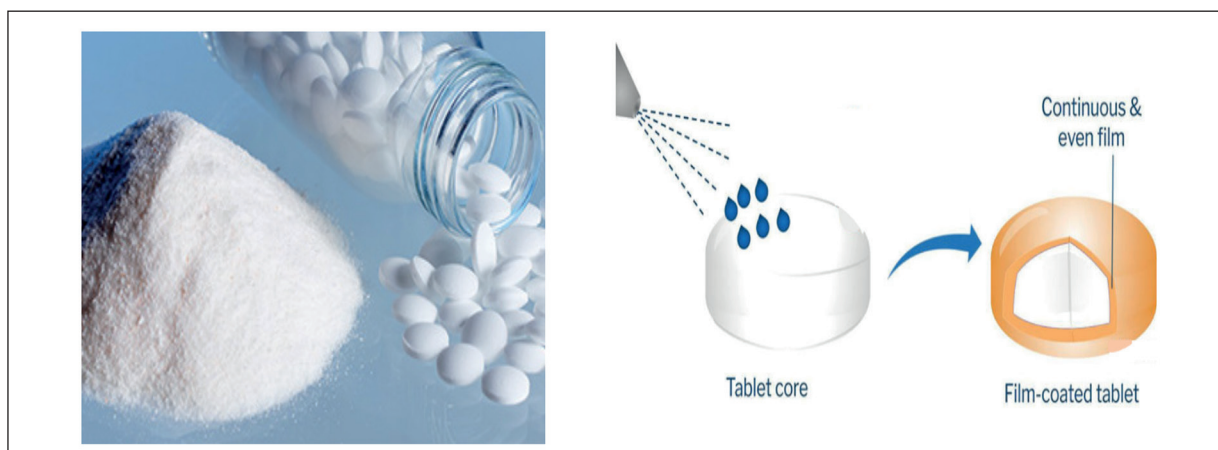


Figure 5. The most possible manufacturing process for Xonvea® 10 mg/10 mg gastro-resistant tablets.

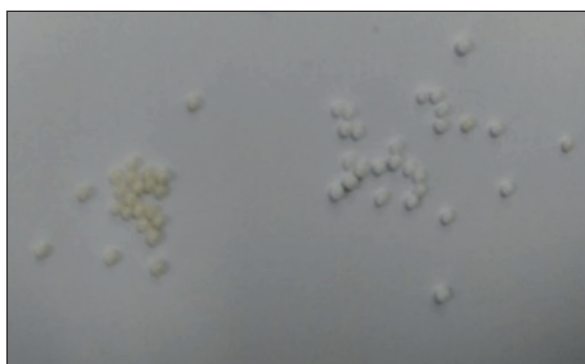


Figure 6. Two population of pellets or microgranules contained into Cariban® capsules.

Leaving aside the difference in technology between products, the substantial differences of Cariban® capsules in comparison to Xonvea® tablets are in its composition, since Cariban® includes shellac in addition to the same functional

polymer [Methacrylic acid-ethyl acrylate copolymer (1:1)]. Shellac is an excipient used in the pharmaceutical industry for its modified release characteristics being different from the functional polymer because is not sensitive to pH change. So, the combination of both excipients confers a quite different release characteristic than Xonvea® tablets.

However, the different technology used, the difference in composition and the differences in the dosage forms of pyridoxine/doxylamine fixed dose combinations seem to have an important role with respect to the behaviour of capsules versus tablets

The *in vitro* dissolution behavior of the two formulations, Cariban® 10 mg/10 mg modified-release hard capsules and Xonvea® 10 mg/10 mg gastro-resistant tablets, have been studied. Dissolution media have been designed to mimic the *in vivo* conditions. According to the reviewed pharmacokinetics data, Xonvea® seems to show

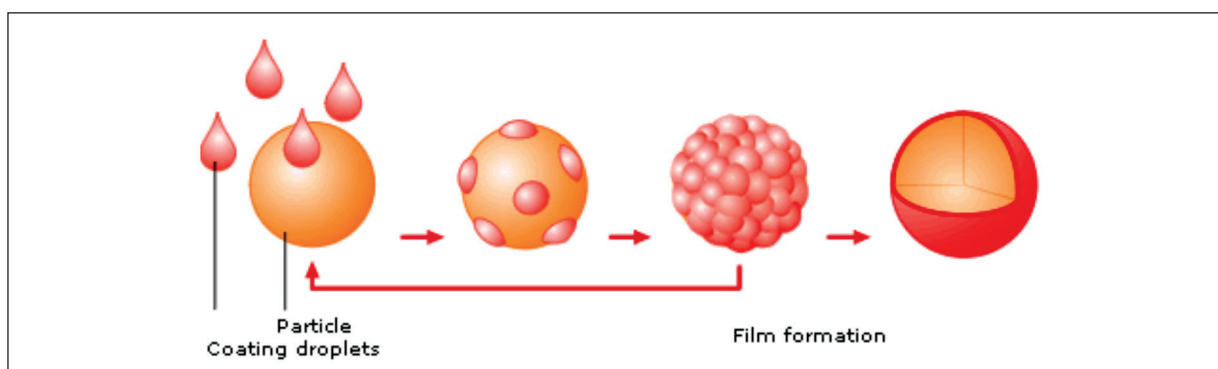


Figure 7. The most possible manufacturing process for Cariban® 10 mg/10 mg modified-release capsules.

a higher absorption rate (greater C_{max}) compared to Cariban® for Pyridoxine. Dissolution data obtained are aligned with the pharmacokinetic results. Dissolution of Xonvea® gastro-resistant tablets is faster and complete at pH 6.8 compared to Cariban® capsules. This could explain the greater C_{max} observed *in vivo* for the gastro-resistant tablets formulation. This could translate into a differential onset of action and relief of nausea for pregnant women taking the tablets vs. the capsules.

The limitation of the study is that this *in vitro* data cannot automatically correspond to *in vivo* data as it is an experimental approach regarding pharmacological aspects.

Nevertheless, as the dissolution speed of Xonvea® gastro-resistant tablets is superior and more rapidly complete at pH 6.8, translating into a greater C_{max} and quicker T_{max} than prolonged-release granules of Cariban® contained into capsules, it can be supposed that a similar reaction occurs in the human gastrointestinal tract.

Conclusions

At pH 6.8, complete and faster release of the fixed dose combination for Xonvea® gastro-resistant tablets compared to Cariban® capsules could possibly explain the greater C_{max} observed *in vivo* for the tablets' formulation. This could translate into faster onset of action and relief of nausea for pregnant women taking the tablets vs. the capsules.

Conflict of Interest

The authors are employees of Insud Pharma.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

Availability of Data and Material

On request to the authors.

Funding

Not applicable.

Authors' Contribution

Cristina Alcocer: Design and conceptualisation, laboratory analyses. Maite Iraola: Validation, laboratory analyses. Eugenia Rom: Responsible for literature research. Didier Horarau: Laboratory analyses, data acquisition. Esteban Geric: Laboratory analyses. Maria Angeles Perez de la Cruz: Writing of the manuscript. Pedro-Antonio Regidor: Responsible for the coordination of the manuscript.

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