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Improvement of cefpodoxime proxetil oral absorption in rats by an oil-in-water submicron emulsion

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Abstract

Absolute bioavailability of cefpodoxime proxetil is both limited by its low solubility in aqueous solution and its intraluminal hydrolysis. The oil-in-water submicron emulsion was proven to be effective in protecting the prodrug from the enzymatic attack in rabbit intestinal washings. The aim of the study was to perform a pharmacokinetic study in conscious rats to confirm o/w submicron superiority in comparison to other oral formulations (hydro-alcoholic solution, suspension and coarse emulsion).

The pharmacokinetic study was performed in conscious rats implanted with permanent aortic catheters. A parenteral solution of cefpodoxime was injected via this catheter, and oral formulations were administered orally. The cefpodoxime plasma level was performed by a HPLC validated method. The pharmacokinetic parameters, $t_{1/2}$, C_{max}, t_{max}, AUC and absolute bioavailability (F) were determined with a non-compartmental analysis. The results show a significant increase of F for submicron emulsion (97.4%) between the other oral formulations. No significant difference of F was found between the other oral formulations, even with the coarse o/w emulsion.

The o/w submicron emulsion made the enhancement of the absolute bioavailability of cefpodoxime proxetil possible. This benefit could be explained by the low droplet size of the submicron emulsion which improve the absorption process of the prodrug.

Keywords: Bioavailability; Cefpodoxime proxetil; Oral emulsions; Submicron o/w emulsion; Conscious rat

1. Introduction

Cefpodoxime proxetil is an orally absorbed, broad spectrum, third generation cephalosporin ester. This prodrug ester is hydrolyzed in vivo into its active metabolite named cefpodoxime. In humans, the absolute bioavailability of cefpodoxime is about 50% after the administration of cefpodoxime proxetil as a 132 mg tablet (equivalent to 100 mg of cefpodoxime) (Borin, 1991). Previous studies realized in vitro, in rabbit and human duodenal washings (Crauste-Manciet et al., 1997a,b) have shown that cefpodoxime proxetil was hydrolyzed by a cholinesterase prior to its intestinal absorption. These results may explain its incomplete absorption.

Oil-in-water (o/w) submicron emulsion was previously found to be effective in protecting the prodrug from enzymatic attack in rabbit duodenal washings (Crauste-Manciet et al., 1998).

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The aim of this work was to study the bioavailability of cefpodoxime in rats after oral administration of cefpodoxime proxetil in different formulation which are: o/w coarse emulsion, o/w submicron emulsion, suspension and hydro-alcoholic solution.

2. Materials and methods

2.1. Materials

Cefpodoxime proxetil was kindly provided by Roussel Uclaf (Romainville, France). Medium-chain-triglycerides (MCT) of caprylic and capric acids (Miglyol 812N®) were provided by Condea (Witten, Germany). Blends of mono-(50%), di-(40%) and triesters (8%) of caprylic and capric acids (Inwitor 742®) were supplied from Hüls (Marl, Germany). Soybean lecithin (Lipoïd S40®) was provided by LipoïdKG (Ludwigshafen, Germany). Polysorbate 80 (Montanox 80®) was purchased from Seppic (Paris, France). Carmellose (Blanose 7HF®) was provided by Coopérative Pharmaceutique Française (Rueil Malmaison, France). All the other reagents were of pharmaceutical grade.

2.2. Methods

2.2.1. Formulation preparation

2.2.1.1. Parenteral solution. The cefpodoxime (final concentration 3.06 mg/ml) was dissolved in an aqueous solution containing 0.9% of sodium chloride. The solution was sterilized through a 0.22 μm filter under a laminar airflow hood. Cefpodoxime final concentration in parenteral solution was equivalent to 4 mg/ml of the prodrug (cefpodoxime proxetil) which was used in all the oral formulation.

2.2.1.2. Emulsions. The cefpodoxime proxetil was first dissolved in the cosolvant, Inwitor 742®, and the mixture was dissolved in MCT oil. Lecithin was dissolved in both oil and aqueous phase. Both phases were then mixed and emulsified by a phase inversion method (Becher, 1965) using a high shear mixer (Ultraturrax, Ika Werk, Staufen, Germany). This first emulsion preparation step gave a coarse o/w emulsion. To perform a submicron emulsion, the former coarse emulsion was rapidly cooled and homogenized using a two-stage high pressure valve homogenizer Rannie (Mini-lab, Wesfalia separator, Chateau-Thierry, France).

Table 1
Composition (w/w) of the investigated oral formulations incorporating cefpodoxime proxetil (4 mg/ml final concentration)

	o/w emulsions	Hydro-alcoholic solution	Suspension
Miglyol 812N®	12	–	–
Inwitor 742®	8	–	–
Lipoïd S40®	1.2	–	–
Ethanol 95% (v/v)	–	8	–
Citric acid	–	8.4	–
Blanose 7HF®	–	–	0.35
Montanox 80®	–	–	0.2
Water qs	100	100	100

2.2.1.3. Hydro-alcoholic solution. The hydro-alcoholic solution was prepared according to the literature data (Borin et al., 1995). The cefpodoxime proxetil was first dissolved in ethyl alcohol (95% v/v) and the mixture was then added to an aqueous solution containing citric acid.

2.2.1.4. Suspension. The suspension was obtained by adding the cefpodoxime proxetil and the Blanose 7HF® into a shear mixer containing an aqueous solution of Montanox 80®. The composition of the investigated oral formulations are listed in Table 1.

2.2.2. Emulsion characterization

2.2.2.1. Particle size analysis. The mean droplet size and particle size distribution of coarse and submicron emulsion were determined by a laser diffraction particle size analyzer (Mastersizer®, Malvern, Orsay, France). Each emulsion sample was diluted in water to an appropriate concentration before measurement at 25 °C. The particle size distribution is given in Fig. 1.

2.2.2.2. ξ-Potential. *ξ-Potential* which measures surface droplet charge was performed to assess stability of emulsions. It was measured using the moving boundary electrophoresis technique. Each emulsion sample was diluted with 10 mM HEPES buffer (1:2000) prior to examination. The ξ-potential values of every emulsion sample were obtained using the Malvern Zetamaster® (Malvern, Orsay, France).

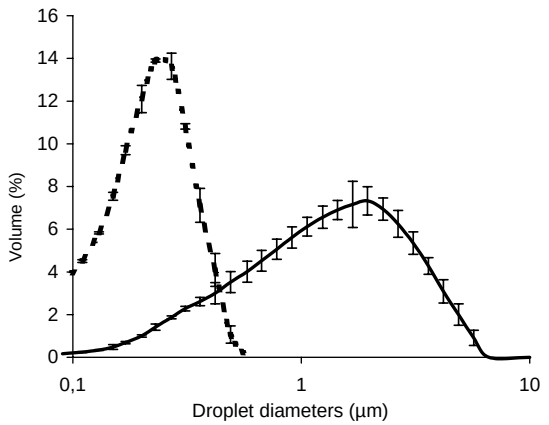

Fig. 1. Particle size distribution of coarse (—) and submicron (- - -) emulsions. Results are mean ± S.D. error bar of three determinations.

2.2.2.3. pH. The pH of the emulsion samples was measured using a pH meter (HI 9318, Hanna, Prolabo, Paris, France). Characteristics of the o/w emulsions are shown in Table 2. According to the same composition of both emulsions, only mean droplet size was different. Same pH values and negative ξ-potential were found for both emulsions. Negative charge measured in both cases comes from negative ionized phospholipids included in soybean lecithin emulsifier. Negative droplet charge contributes to improvement of long term stability of both emulsions.

2.2.3. In vivo absorption study

2.2.3.1. Rat experimentation. The pharmacokinetic study was realized in conscious adult male Wistar rats, weighing 100–150 g according to the Waedele and Stoclet method (Waedele and Stoclet, 1973). The study was performed on nine rats for the parenteral solution and six rats for the oral galenic forms. Prior to surgery, anesthesia was performed on the rat by an intraperitoneal injection of pentobarbital, then a polyethylene catheter was permanently implanted into the thoracic aorta through the left carotid. The free end of the catheter was externalized at the base of the neck and covered with a small rubber plug allowing to clamp the cannula. After the surgery, rats were placed in restraining cages. Blood sampling and parenteral solution injection were realized via this cannula. Before and between every blood sampling, the catheter was filled with a viscous solution (40% polyvinylpyrrolidone and calcium heparinate 5000 IU/ml). Rats were fasted for 24 h prior to the experiment and fasted for more than 12 h. However, a free access to water was allowed throughout the experiment.

Table 2
Oil-in-water emulsion characteristics

	Coarse emulsion	Submicron emulsion
Mean droplet size (μm)	2.41 ± 0.03	0.230 ± 0.006
ξ-Potential (mV)	−72.37 ± 2.73	−62.42 ± 0.58
pH	6.01 ± 0.01	5.96 ± 0.02

Results are mean ± S.D. of three determinations.

Oral formulations were delivered by an oral intubation cannula. Parenteral solution was injected through the catheter. The cefpodoxime dosage was 20 mg/kg whatever the galenic form.

During each experiment, 0.3 ml of blood was collected from the catheter and put into heparinized tubes at 15, 30, 45, 60, 90, 120, 180, 300 min for parenteral ($n = 9$) and oral ($n = 6$) formulations. Because of the sustained release of the emulsions and the suspension formulations, their time analysis was insufficient. Therefore, another pharmacokinetic study was performed for these formulations ($n = 6$). For this study, blood was collected at 45, 60, 120, 180, 240, 360, 480, 600 min. A 3 day wash-out period was respected between all pharmacokinetic experiments.

2.2.3.2. HPLC analysis of cefpodoxime plasma level. The level of cefpodoxime in plasma samples was measured by a sensitive and specific HPLC method with UV detection (Camus et al., 1994).

Each plasma sample was first diluted (1/3) with an internal standard solution (ceftriaxone 10 μg/ml, Sigma, Saint-Quentin Fallavier, France), eluted through a silica column (Bond elut C8, 500 mg/3 ml, Varian, Paris, France) in order to adsorb cefpodoxime which is then desorbed and recovered with methanol. 50 μl of the eluted phase was then analyzed through an optimized system composed by a Supelcosil LC18 (250 mm × 4.6 mm, 5 μm particle size) column (Supelco, Saint Germain-en-Laye, France), and a ternary mobile phase acetate buffer 0.05 M, pH 3.8/methanol/acetonitrile 87:10:3 (v/v/v). The flow rate was 1 ml/min and the separation was carried out at ambient temperature and monitored at 235 nm. The linearity, and both between- and within-day

reproductibility, were assessed. The inter-assay and intra-assay coefficient of variation were within the range of 10.4–3.3 and of 9.6–3.6% for cefpodoxime concentrations between 1 and 100 μg/ml, respectively. For this HPLC method, the limit of quantification was 0.2 μg/ml.

2.2.3.3. Pharmacokinetic parameter analysis. Cefpodoxime pharmacokinetic parameters were determined with a non-compartmental analysis (Gibaldi and Perrier, 1982), except the C_0 of the parenteral solution which was estimated with a bicompartmental model. Elimination rate constant (k_e) was estimated by linear least-square regression on the final plasmatic concentrations of cefpodoxime (Fig. 2). The half-life of elimination ($t_{1/2}$) was calculated with the following equation: $t_{1/2} = \ln 2/k_e$. For oral administration: C_{max} and time to reach C_{max} (t_{max}) were determined through the observation of individual animal concentrations versus time curves. Mean resident time (MRT) was calculated with the following formula: $\mathrm{MRT} = \int_{(0-\inf)} t \times C_t \, dt / \int_{(0-\inf)} C_t \, dt$. The mean absorption time (MAT) was calculated with the following formula:

$$\mathrm{MAT} = \mathrm{MAT_o} - \mathrm{MAT_{iv}}$$

where $\mathrm{MAT_o}$ was the oral route and $\mathrm{MAT_{iv}}$ was the intravenous route.

The area under the plasma concentration curve (AUC) was calculated with the trapezoidal rule and an extrapolation to infinite. All extrapolations of AUC were under 20%. The AUC from the last experimental time to infinity ($\mathrm{AUC}_{t\to\infty}$) was calculated by dividing the last measured plasma concentration value by the elimination rate constant (k_e). The total AUC was calculated as the sum of $\mathrm{AUC}_{0\to t}$ and $\mathrm{AUC}_{t\to\infty}$. The absolute bioavailability F of the oral dosage forms was estimated as the $\mathrm{AUC}_{0\to\infty}$ ratio of the oral dosage form to the parenteral solution.

2.2.3.4. Statistical analysis. A Mann–Whitney test was used in order to compare t_{max}, and an ANOVA test was used in order to compare the other pharmacokinetic parameters. Statistical significance was defined as $P < 0.05$.

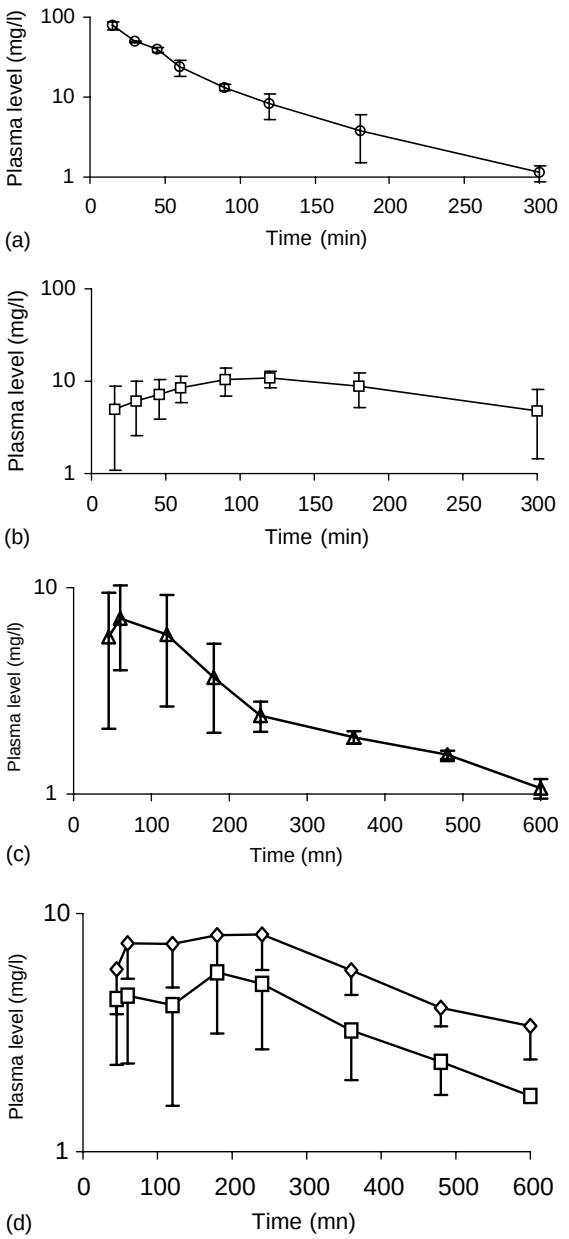

Fig. 2. Cefpodoxime plasma level concentration after administration of parenteral solution (○) ($n = 9$) (a), hydro-alcoholic solution (□) ($n = 6$) (b), suspension (△) ($n = 6$) (c), submicron emulsion (◇) ($n = 6$), and coarse emulsion (□) ($n = 6$) (d). Results are mean ± S.D. error bar.

Table 3
Pharmacokinetic parameters of oral formulations

Pharmacokinetic parameters	Oral formulations			
	Solution	Suspension	Coarse emulsion	Submicron emulsion
C_{max} (μg/ml)	12.2 ± 3.7	8.1 ± 2.8	6.3 ± 2.6	9.1 ± 2.9[a]
t_{max} (min)	120 ± 37	78 ± 27	190 ± 45	200 ± 49[b]
$t_{1/2}$ (min)	85 ± 33	164 ± 29	143 ± 33	320 ± 183[c]
k_e ($\times 10^{-3}$ min^{-1})	9.3 ± 3.7	4.3 ± 0.7	5.1 ± 1.2	2.8 ± 1.7[c]
MAT (h)	1.75 ± 0.50	3.75 ± 1.50	4.35 ± 1.00	8.95 ± 1.60[d]
MRT (h)	2.8 ± 0.5	4.8 ± 1.2	5.4 ± 1.0	10.0 ± 1.6[d]
Cl (ml/min)	0.50 ± 0.17	0.39 ± 0.07	0.57 ± 0.25	0.43 ±0.09[d]
$AUC_{0\to\infty}$ (μg min/ml)	2643 ± 923	2074 ± 511	2762 ± 873	4272 ± 719[d]
F (%)	60.3 ± 21.0	47.3 ± 11.7	62.2 ± 19.7	97.4 ± 16.8[d]

Results are mean ± S.D. of six determinations (except parenteral solution, $n = 9$).
[a] Non-significantly different from paired solution, suspension and coarse emulsion.
[b] Significantly different ($P < 0.05$) from paired solution and suspension.
[c] Significantly different ($P < 0.05$) from paired solution and coarse emulsion.
[d] Significantly different ($P < 0.05$) from paired solution, suspension and coarse emulsion.

3. Results

Pharmacokinetic parameters obtained after intra-aortic injection of cefpodoxime ($n = 9$) show a constant of elimination k_e of $16.5 \times 10^{-3} \pm 2.6 \times 10^{-3}$ min^{-1}, an elimination half-time $t_{1/2}$ of 42 ± 6.6 min, a MRT of 1.05 ± 0.27 h, a clearance of 0.46 ± 0.03 ml/min, a C_0 of 111 ± 11 μg/ml and a $AUC_{0\to\infty}$ of 4383 ± 317 μg min/ml. Pharmacokinetic parameters obtained after oral administration of cefpodoxime proxetil are listed in Table 3.

The values of C_{max} of suspension, coarse emulsion and submicron emulsion are equivalent. C_{max} of the hydro-alcoholic solution is significantly higher than the suspension ($P < 0.05$) and the coarse emulsion ($P < 0.01$). This difference may be due to fastest absorption rate of dissolved drug. At the same time, t_{max} is significantly higher for emulsions in comparison to the other galenic forms ($P < 0.05$), and the t_{max} of hydro-alcoholic solution is higher than the t_{max} of suspension. There is no significant difference between the AUC of hydro-alcoholic solution and suspension or coarse emulsion. Their absolute bioavailabilities are of the same order. In contrast, submicron emulsion presents a significant increase of its AUC compared to the other oral formulations. Furthermore, the AUC of the submicron emulsion is not significantly different from that of parenteral solution. The $t_{1/2}$ and k_e of oral galenic forms are significantly higher than those of parenteral form ($P < 0.05$). However, clearances are not significantly different between per os and parenteral formulations. Cefpodoxime elimination is the same whatever the formulation and the way of administration.

The $t_{1/2}$, k_e of suspension and coarse emulsion are significantly higher than those of hydro-alcoholic solution ($P < 0.05$). The MAT and MRT of submicron emulsion are significantly higher than those of other oral formulations ($P < 0.05$), and there is no difference between them.

4. Discussion

Lipophile prodrugs such as cefpodoxime proxetil are generally incompletely absorbed. This is essentially due to a partial solubilization of the drug in aqueous phase in the intestinal lumen and to enzymatic hydrolysis prior to absorption (Crauste-Manciet et al., 1997a). We found that the submicron emulsion shows the greater absolute bioavailability, which is even equivalent to the parenteral solution value.

The pharmacokinetic parameters of cefpodoxime calculated from the parenteral solution plasma concentrations are similar to those reported by Klesel et al. (1992) after subcutaneous administration in rats, except for the AUC. These authors have effectively found a mean AUC which is 37% smaller (2772 ± 552 μg min/ml) than the one reported in our study. The difference can be explained by the different route of

administration and by the lack of infinite extrapolation of AUC ($AUC_{0\rightarrow 4\,h}$).

Other authors have searched for a way to increase absorption of these drugs by their solubilization and incorporation into a hydro-alcoholic phase (Borin et al., 1995) or in an oily phase (Wagner et al., 1966).

With the same composition of hydro-alcoholic solution, Borin et al. (1995) reported for cefpodoxime an absolute bioavailability of 61% in humans which is of the same order as our results in rats (51%). The different values of t_{max} observed between the hydro-alcoholic solution and the suspension can be explained by the cefpodoxime proxetil solubility which depends on pH. Cefpodoxime proxetil solubility is high (15 mg/ml) at very low pH (0.7) and fast decreases at higher pH. Solubility is 4 mg/ml at pH 2, 0.4 mg/ml at pH 7 (Hamaura et al., 1995a,b) and 0.26± 0.06 mg/ml at pH 8 ($n = 3$, personal data). Duodenal pH which is 5.5–6.5 (Rouges et al., 1996) could decrease cefpodoxime proxetil solubility and delay absorption of the prodrug.

Emulsion formulations usually allow an increase of absorption in comparison to an oily solution (Wagner et al., 1966; Kararli et al., 1992; Uno et al., 1999). Previous studies were generally performed with coarse emulsions for which the particle size distribution is not always reported. Some studies show the benefit of the submicron emulsion (Kararli et al., 1992; Uno et al., 1999) in comparison to other oral formulations. In our study no benefit on bioavailability of the coarse emulsion was observed, neither for the suspension nor for the hydro-alcoholic solution. These results show that as long as the drug is incorporated in the emulsion oily phase, the absorption process time is increased. This increase of t_{max} and $t_{1/2}$ such as the decrease of C_{max} prove that favor a mediated release of the drug. Also apparent $t_{1/2}$, and k_e of submicron emulsion are higher than that of other oral formulations, but there is no significant difference with the suspension. The similarity of absolute bioavailability for all these three formulations may suggest that the limiting factor of the absorption process is not only the drug solubilization.

The superiority of the submicron emulsion on the coarse emulsion may be explained by the absorption process of lipids. Various hypotheses put forward on the mechanisms of digestion and lipids absorption tend to demonstrate the major impact of droplet size on absorption and enable us to explain the differences observed between submicron and coarse emulsions. A comparison of emulsions of different sizes demonstrated the benefit on absorption for drugs incorporated into emulsions with droplets with the lowest medium diameter (Toguchi et al., 1990). One of the first steps of lipid digestion is the enzymatic attack by gastric and pancreatic lipase (Embleton and Pouton, 1997). This enzymatic attack is directly correlated to the specific surface area (Mac Gregor et al., 1997). The greater the area, the greater and more efficient the enzymatic attack. According to Kakemi et al. (1972), the total specific surface area of the oil droplets of an emulsion can be calculated by the following equation: $S = 6V/R$ (where S is the total surface area of oil droplets, V is the total volume of oil droplets and R is the mean diameter of an oil droplet). In the case of our emulsions, the submicron emulsion has a surface area which is ($S = 52{,}173\,cm^2$) 10-fold greater than the coarse emulsion ($S = 4979\,cm^2$); this could explain the difference of bioavailability of the drug between the submicron emulsion and the coarse emulsion. Moreover, intragastric and duodenal lipolysis is significantly greater with the submicron emulsion than with the coarse emulsion (Armand et al., 1999). The better lipid digestion of the submicron emulsion could explain the better absorption of the drug.

Former studies performed in vitro on rabbit intestinal washings (Crauste-Manciet et al., 1998) showed that the submicron emulsion was able to protect the cefpodoxime proxetil significantly against intestinal lumen enzymatic hydrolysis. Intestinal lumen protection against hydrolysis by emulsion formulation is not a relevant explanation. Because the coarse emulsion was not able to enhance prodrug absorption, droplet size may play a major role in the enzymatic degradation. It could be related to the less efficient lipid digestion of the coarse emulsion.

In the second phase of digestion, mixed micelles are formed by the action of biliar salts (Toguchi et al., 1990). This phase is also influenced by the specific surface area (Mac Gregor et al., 1997). The drug in the oily phase is more incorporated into mixed micelles when the specific surface area of the emulsion is important.

The degradation products of lipid digestion, like fatty acids, can be absorbed by the lymphatic route. This route of absorption can also apply to dissolved drugs incorporated into oily phases (Embleton and

Pouton, 1997). When a drug is incorporated into a submicron emulsion, droplets can be directly absorbed owing to their low size. Studies (Desaï et al., 1996) on nanocapsule absorption have described how lymphatic absorption was preferential for those with the smallest diameters (between 100 an 500 nm). Moreover, another study (Uno et al., 1999) has demonstrated the benefit of absorption of a submicron emulsion containing tacrolimus correlated with the direct uptake by the reticulo endothelial system. An amount of cefpodoxime proxetil included in the submicron emulsion (mean diameter 230 nm) could also be absorbed via this route. Improvement of absorption with the submicron versus coarse emulsion can be explained by the difference of their droplet sizes. This observation demonstrates the effect of lowest droplet size on digestive absorption of drugs administered in dispersed oral formulations.

In conclusion, the aim of this study was to appreciate in vivo, in rats, the benefit of bioavailability of the galenic optimisation of a prodrug ester: cefpodoxime proxetil with a limited oral bioavailability.

Of the oral formulations evaluated (hydro-alcoholic solution, suspension, emulsions), only the submicron emulsion allowed a significant increase of drug bioavailability. Knowing that both the coarse emulsion and the submicron emulsion have the same composition, this shows that the droplet size plays a major role on the absorption process of cefpodoxime proxetil.

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