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Research paper

Ordered mesoporous silica to enhance the bioavailability of poorly water-soluble drugs: Proof of concept in man

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ABSTRACT

Formulating poorly water soluble drugs using ordered mesoporous silica materials is an emerging approach to tackle solubility-related bioavailability problems. The current study was conducted to assess the bioavailability-enhancing potential of ordered mesoporous silica in man. In this open-label, randomized, two-way cross-over study, 12 overnight fasted healthy volunteers received a single dose of fenofibrate formulated with ordered mesoporous silica or a marketed product based on micronized fenofibrate. Plasma concentrations of fenofibric acid, the pharmacologically active metabolite of fenofibrate, were monitored up to 96 h post-dose. The rate (C_{max}/dose increased by 77%; t_{max} reduced by 0.75 h) and extent of absorption (AUC_{0-24h}/dose increased by 54%) of fenofibrate were significantly enhanced following administration of the ordered mesoporous silica based formulation. The results of this study serve as a proof of concept in man for this novel formulation approach.

1. Introduction

Ordered mesoporous silica (OMS) materials have recently emerged as carriers for the oral delivery of poorly water-soluble drugs. These materials are mesoporous, meaning that the pore diameter is between 2 and 50 nm (IUPAC definition), and ordered in crystallographic sense meaning that the mesopores are uniform in size and organized in a regular manner in the silica matrix which itself is amorphous.

Deposition of an active pharmaceutical ingredient (API) in the mesopores of the carrier, typically conducted via solvent-based impregnation techniques, is associated with a suppression of recrystallization of the entrapped molecules by virtue of finite-size effects [1] and as such mesoporous silica materials are excellent stabilizers for amorphous APIs [2–4]. When a mesoporous silica material loaded with a poorly water-soluble API is exposed to aqueous media, the release rate of the API from the silica material is typically faster than the dissolution rate of crystalline form [2] and often associated with the generation of a supersaturated API solution [5–7] which offers the potential to increase bioavailability as demonstrated in non-clinical models for drugs such as itraconazole [8,9], glibenclamide [6] and ezetimibe [3].

Some of us have developed an OMS material which is very convenient in terms of its synthesis [10] and suitable for the delivery of poorly water-soluble drugs [3]. A very recent paper from our group reported on the use of this OMS material for the bioavailability enhancement of the poorly soluble API fenofibrate in beagle dogs [11]. The present study was set up to complement these promising findings with in vivo data in man. To the best of our knowledge, no prior papers have reported on the oral administration of ordered mesoporous silica based formulations in man.

Fenofibrate is a non-ionizable compound and exhibits low solubility over the entire physiological pH range [11]. It is a lipid-regulating agent, indicated for the treatment of primary hyperc-

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holesterolemia, mixed dyslipidaemia or types IV and V hypertriglyceridemia [12]. Fenofibrate is rapidly and efficiently absorbed from the gastrointestinal tract and quantitatively converted to its pharmacologically active metabolite fenofibric acid prior to entering the systemic circulation [13]. Fenofibric acid is highly bound (>99%) to plasma proteins and excreted primarily as glucuronide in the urine (70% in 24 h and 88% in 6 days) [13].

A variety of enabling formulations of fenofibrate are being commercialized. One such formulation is Lipanthyl®, a capsule-based dosage form based on micronized fenofibrate. In the current study, the biopharmaceutical performance of fenofibrate loaded onto an OMS material was compared against the marketed formulation Lipanthyl® by measuring the systemic exposure to fenofibric acid following oral administration to fasted, healthy human volunteers.

2. Materials and methods

2.1. Formulations

Fenofibrate was loaded onto the OMS material (details on the synthesis and characteristics of this material can be found in [10]) at a 29% loading, and subsequently blended with a diluent and a disintegrant and filled into size 00 hard gelatin capsules as previously described [11]. Additional information on the characterization, in vitro performance and physical and chemical stability of the OMS-based formulation is also published elsewhere [11]. The total fenofibrate dose per capsule was 33.5 mg. The OMS-based formulation is referred to hereafter as Fenofibrate-OMS. Lipanthyl® capsules were used without modifications to the original dosage form (size 4 hard gelatin capsules containing 67 mg of micronized fenofibrate).

2.2. Subjects

The clinical trial was conducted at SGS Life Science Services (Clinical Pharmacology Unit Antwerp, Belgium). Details of the subject population are provided in Table 1.

The subjects were in a good health as assessed by detailed medical history, physical examination, 12-lead electrocardiogram (ECG), clinical laboratory tests and urinary drug screen. All subjects were non-smokers. The time span between the screening visit and the last follow-up visit was at most 6 weeks. Subjects were to discontinue all medications, except occasional paracetamol (maximum dose of 2 g/day and maximum of 10 g/2 weeks), at least 2 weeks prior to the first study drug administration. In addition, subjects were to agree not to use any medications during the course of the study. Subjects were not to take any alcohol and grapefruit-containing foods from 48 h before to 96 h after each study drug administration or xanthine-containing beverages and food from 12 h before to 96 h after each study drug administration. Subjects with a history of hypersensitivity to fenofibrate or a significant allergic reaction to any drug, an immunosuppressive condition, malignancy within the past 5 years, significant blood loss within 8 weeks prior to study start, diseases of the gastrointestinal tract, liver, kidneys or any other conditions known to interfere with the absorption, distribution, metabolism or elimination of drugs were excluded from the study. Individuals with active drug or alcohol abuse within 2 years prior to the initial study drug administration or consumption of large quantities of coffee or tea were also excluded.

All subjects were Caucasian males. The subjects' median (range) age was 46.5 (21–55) years. Their median (range) BMI was 25.20 (20.8–27.8) kg/m^2. There were no relevant differences in demographic data between the treatment sequences. Serology screening tests for hepatitis B and C and HIV, urine drug screening, and alcohol breath tests at screening were negative for all subjects. A wide range of medical history was reported across the subjects; none of these were thought to have influenced the course of the study. Concomitant diseases were reported in 1 subject (16.7%) in each treatment sequence. Both were Gilbert's Disease. Previous medication was reported in none of the subjects and 1 subject (8.3%) was administered Ditemer (tetanus, diphtheria vaccine) in Dosing Period 2 due to a head injury reported as an AE in Dosing Period 1.

In each of the two dosing periods, the subjects were admitted to the clinical centre on Day -1 and remained hospitalized until approximately 24 h after dosing (Day 2). Thereafter, subjects were to return to the clinical centre on Days 2 (evening), 3, 4, and 5 for post-dose bioanalysis blood sampling. A follow-up visit was planned between 5 and 7 days after the last intake of study drug. The two dosing periods were separated by a 7-day wash-out period. All study drug intakes occurred under the supervision of the investigator or his designee. The study drugs were administered between 8 and 10 a.m. In each dosing period, the subjects received an evening meal on Day -1, at least 9 h before intake of study drug, and a lunch, snack, and evening meal on Day 1. During confinement at the clinical centre, no food intake other than the standard meals was authorized. On the days of blood sampling for bioanalysis water intake was prohibited from 2 h pre-dose until 2 h post-dose, with the exception of the water intake of 200 mL with dosing. Water was available ad libitum from 2 h post-dose onwards. Subjects who discontinued the study prior to completion of the scheduled study procedures for reasons such as adverse events (AE) or withdrawal of consent were invited for a follow-up visit 5–7 days after the last study drug intake. In case of an AE, the appropriate follow-up procedure was applied.

Table 1
Demographic data by treatment sequence (safety population).

Parameter	Sequence AB N = 6	Sequence BA N = 6	All subjects N = 12
Age, years			
Median (range)	49 (40–55)	43 (21–49)	46.5 (21–55)
Height, cm			
Median (range)	178 (168–192)	180 (175–192)	178 (168–192)
Weight, kg			
Median (range)	80.5 (73–101)	80 (66–90)	80 (66–101)
BMI, kg/m^2			
Median (range)	25.9 (24.4–27.4)	24.5 (20.8–27.8)	25.2 (20.8–27.8)
Sex, n (%)			
Male	6 (100)	6 (100)	12 (100)
Race, n (%)			
Caucasian	6 (100)	6 (100)	12 (100)

N = number of subjects; n = number of subjects with that observation; Treatment A: single oral dose of 33.5 mg Fenofibrate-OMS; Treatment B: single oral dose of 67 mg Lipanthyl®.

2.3. Safety monitoring

In each dosing period, subjects underwent a physical examination, an assessment of vital signs and a 12-lead ECG recording on Day 1 pre-dose. Blood and urine sampling for clinical laboratory tests (haematology, serum biochemistry and urinalysis) was performed in fasting conditions. All assessments were performed within 2 h pre-dose. Subjects were discharged from the clinical centre upon agreement of the investigator on Day 2, after safety assessment (blood and urine samples for clinical laboratory tests, ECG, vital signs) and the last blood sampling for bioanalysis. The subjects returned to the clinical centre 5–7 days after the last dose administration for the follow-up visit for a physical examination and vital signs (HR, SBP, DBP, oral body temperature) assessment. Blood and urine samples for clinical laboratory tests were taken in fasting conditions. Any adverse or unusual event occurring from

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