Specific Studies for Formulation Development

Roland Wesch

Contents

Abstract

The bioavailability of a drug depends on the properties of the drug product, a combination of drug and formulation properties. The support for formulation development by means of clinical PK studies is multifaceted and, in fact, covers all routes of administration, intravascular routes as well as extravascular ones, like oral, intramuscular, or subcutaneous routes, and – in most instances – vaginal, dermal, ocular, topic, rectal, nasal, or pulmonary administration. The drugability (disease-tailored exposure profiles mediated by optimized delivery systems) of pharmacologically active substances will remain one of the major challenges in drug development, especially if poorly absorbable, poorly soluble compounds are considered. Rare exceptions include some drugs belonging to BCS class I (highly soluble, highly permeable) that rapidly dissolve from Immediate Release solid oral drug products.

R. Wesch (✉)
R&D Metabolism and PK Germany, Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany
e-mail: roland.wesch@sanofi.com; Roland.Wesch@sanofi-aventis.com

F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_15-1

Purpose and Rationale

The bioavailability of a drug depends on the properties of the drug product, a combination of drug and formulation properties. The support for formulation development by means of clinical PK studies is multifaceted and, in fact, covers all routes of administration, intravascular routes as well as extravascular ones, like oral, intramuscular, or subcutaneous routes, and – in most instances – vaginal, dermal, ocular, topic, rectal, nasal, or pulmonary administration. The drugability (disease-tailored exposure profiles mediated by optimized delivery systems) of pharmacologically active substances will remain one of the major challenges in drug development, especially if poorly absorbable, poorly soluble compounds are considered. Rare exceptions include some drugs belonging to BCS class I (highly soluble, highly permeable) that rapidly dissolve from Immediate Release solid oral drug products.

Formulation development requires close coordination of various functions, for example, galenics, analytics, process development, preclinical, and clinical pharmacology. Clinical PK is just one, however, an important component in this framework.

Details about how to deal with changes in components or composition of drug products are described in published regulatory guidances (Guidance for Industry Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on the biopharmaceutics classification system (BCS). U.S. Department of Health and Human Services et al. 1999; SUPAC-IR 1995; SUPAC-MR 1997), while no formal guidance exists that in particular covers all types of formulation interactions. Details about clinically relevant (drug–drug) interactions and assessment of equivalence of formulations can be found in Guidance for Industry Statistical Approaches to Establishing Bioequivalence (2001), Steinijans and Hauschke (1997), CPMP (2002), and CPMP (1998).

In order to optimize drug exposure, the development of modified release formulations is an option. In vitro tests (stability testing, dissolution) are routinely used as a first step in formulation development in order to build an absorption model for the prediction of in vivo exposure via the in vitro/in vivo correlation. The assessment of efficacy in disease models and exposure (PK) in animals will be applied to lead candidates only, before going to man.

Reasons for change of formulation include, but are not limited to, poor bioavailability of solid oral formulations, limitations in drug load for oral or parenteral formulations, profound food effect, too early/too late onset of action (absorption, distribution), too short/too long duration of action (metabolism, elimination), or high intra- and inter-individual variability.

Procedure

The design of an exploratory formulation development study with SAR001 is presented below in Part A.

In the project with SAR001, the formulation development study explored the relative bioavailability of three prototype nanocrystal (NC) formulations (tablet, granules, lyophilisate) versus a soft gelatine capsule (SGC) formulation that was used in early clinical phases. This study should help to determine selection and development of alternative formulations to be used in Phase III studies, as the current SGC had *limitations in the unit strength* possibly not suitable for long-term efficacy trials. The food effect was also investigated, as in an animal pilot study, the *magnitude of food effect* was more important for NC dispersion when compared to SGC.

In another project (HMR456) modified release (MR) formulations were developed in order to overcome the *short elimination half-life,* and thus, a *short duration of action* of the Immediate Release formulation. The study design and the main PK results are presented elsewhere in this textbook (food effect chapter). In Part B, we will discuss the value of the deconvolution tool, which was applied to the PK results of the study.

Part A

Protocol Outline

Relative bioavailability of three prototype nanocrystal formulations of SAR001 in comparison to a soft gelatin capsule formulation of SAR001 under fasting and fed conditions to healthy subjects.

Primary Objective

To assess the relative bioavailability of three prototype nanocrystal formulations of SAR001, in comparison to the soft gelatin capsule formulation, by assessing plasma concentration of SAR001 under fasting and fed conditions.

Study Design

Open, randomized, two-group, four-treatment, four-period, four-sequence crossover study using two parallel groups under fasting or fed conditions (Groups I and II, respectively). All single oral drug administration periods within groups were separated by a washout of 7 days.

Inclusion Criteria

Healthy male subjects, aged between 18 and 45 years, with a Body Mass Index (BMI) between 18 and 28 kg/m^2 inclusive, and liver function tests and creatine kinase values within reference ranges.

Treatments

- Treatment A: Single dose of 80 mg SAR001 in soft gelatin capsule (SGC).
- Treatment B: Single dose of 80 mg SAR001 in uncoated tablet.
- Treatment C: Single dose of 80 mg SAR001 in granules for oral suspension.
- Treatment D: Single dose of 80 mg SAR001 as lyophilisate for oral suspension.

All treatments were administered under two food conditions: fasting (overnight fasting + 4 h postdose, Group I) and fed (high fat-high calorie breakfast starting 30 min and ending 5 min predose, Group II).

Pharmacokinetic Data

Concentration of SAR001 in plasma before and at predefined times after dosing.

Evaluation

Only part of the evaluation will be presented here.

Standard descriptive statistics were calculated for each parameter and each treatment.

To determine the relative bioavailability of any pair of formulations, 90% confidence intervals (CI) of formulations ratio for $AUC_{0–168}$ and C_{max} were displayed under each food regimen.

For C_{max}, $AUC_{0–72}$, and $AUC_{0–168}$, formulation effect was assessed using a linear mixed effects model separately for each food regimen on log-transformed parameters. Estimates with 90% confidence intervals of pairwise formulations ratio of geometric means were computed within the linear mixed effects model framework.

Similarly, food effect was assessed for each formulation using a linear mixed effects model on log-transformed parameters. Estimates and 90% confidence intervals of food regimens ratio of geometric means were computed within the linear mixed effects model framework.

To determine the food effect on each of the four formulations, 90% CI of fed/fasted ratio for $AUC_{0–168}$ and C_{max} were displayed for each formulation separately.

Critical Assessment of the Method

Due to the exploratory pilot character of such a formulation development study, a sample size calculation in its proper sense is not routinely performed. Often, a number of 12 study completers per cohort is considered sufficient for this purpose. This quite small cohort size "encourages" to implement high complexity with multiple objectives within a single trial. If solid formulations are to be compared, the same unit strength for each formulation is recommended in order to avoid an intrinsic source of variability, for example, if two tablets with 40 mg each are compared to a single capsule with 80 mg drug load. The

number of dose units should be kept low, again to avoid a source of variability. Standardization is questionable if up to ten units or even more have to be swallowed with a limited amount of non-carbonated water (e.g., 240 mL).

Preceding studies should help to define the necessary washout period in order to avoid carry-over effects. If the predose concentration is higher than 5% of C_{max} in a given study period, the predose value should be subtracted from all post-dose concentrations as corrective action.

Concerning food, not only composition (constituents, calories) but also start and end of food intake in relation to drug administration should be standardized.

In this example, the study subjects were stratified for food condition, which results in four high fat-high calorie meals for members of Group II, and in four 14 h lasting fasting periods for members of Group I. In order to avoid late dropouts in crossover studies that apply within comparisons of both food conditions, it may be advisable to define the compliance to high fat-high calorie breakfast as an inclusion criterion for the study.

In all studies with parallel groups, care should be taken that baseline demographics – for example, gender ratios, body weight, BMI, age – are similar between groups. A possibility to overcome this request is the implementation of the same reference treatment for each group. An example for this approach can be found in the food effect chapter.

Modifications of the Method

If in late clinical development the need for a formulation switch becomes evident, and a formulation comparison is necessary for bridging purposes, the exploratory character of a formulation development study gets lost and a bioequivalence study has to be conducted.

Part A

To illustrate the type of data that can be obtained using the discussed study, a high-level summary of the pharmacokinetic results obtained from the study described above under "Procedure" is presented below (Tables 1 and 2; Figs. 1 and 2).

Results – Pharmacokinetics

In fasting or in fed condition, whatever the formulation, t_{max} was about the same, with median values ranging from 2 to 4 h post administration.

In fasting condition, SAR001 exposure was lower with nanocrystal formulations compared to soft gelatin capsules (SGC). In comparison to SGC, variability of pharmacokinetic parameters was similar for the lyophilisate, slightly higher for the tablets and higher for the granules.

In fed condition, SAR001 exposure was close to that observed with SGC for granules and lower than that observed with SGC for tablets. Variability of pharmacokinetic parameters was about the same, whatever the formulation.

Food effect (relative bioavailability) based on $AUC_{0–72}$ was about twice as high with nanocrystal formulations compared to soft gelatin capsules.

Part B

Procedure

The immediate release PK properties of the active metabolite HMR123 of drug HMR456 were not sufficient to support a twice-a-day dosing (terminal elimination half-life too short, time above PD concentration threshold too short). Therefore modified release (MR) formulations were developed. The use of a deconvolution tool will be discussed in this section.

The design of the exploratory bioavailability study on modified release drug products is presented in brief below. Detailed information is given in the food effect chapter. For the assumptions of the hypothetical deconvolution tool, in vitro/in vivo dissolution data from a predecessor study with the same compound was used.

Table 1 Pharmacokinetic population: numbers by treatment/condition

Condition/ treatment	Soft gelatin capsules	Granules for oral suspension	Lyophilisate for oral suspension	Uncoated tablets
Fasting	13	13	13	13
Fed	13	14	13	12

Table 2 Relative bioavailability estimates and 90% confidence intervals between food conditions

Parameter	Food comparison	Ratio estimate and 90% CI
C_{max} (ng/mL)	Fed vs. fasted for capsule	2.03 (1.39, 2.96)
	Fed vs. fasted for granule	4.35 (2.99, 6.32)
	Fed vs. fasted for lyophilisate	5.04 (3.45, 7.35)
	Fed vs. fasted for tablet	5.77 (3.94, 8.47)
$AUC_{0–72}$ (ng·h/mL)	Fed vs. fasted for capsule	2.00 (1.44, 2.76)
	Fed vs. fasted for granule	3.93 (2.85, 5.43)
	Fed vs. fasted for lyophilisate	4.31 (3.11, 5.96)
	Fed vs. fasted for tablet	4.59 (3.31, 6.36)
$AUC_{0–168}$ (ng·h/mL)	Fed vs. fasted for capsule	2.07 (1.54, 2.77)
	Fed vs. fasted for granule	3.85 (2.84, 5.22)
	Fed vs. fasted for lyophilisate	3.69 (2.72, 4.99)
	Fed vs. fasted for tablet	3.86 (2.81, 5.31)

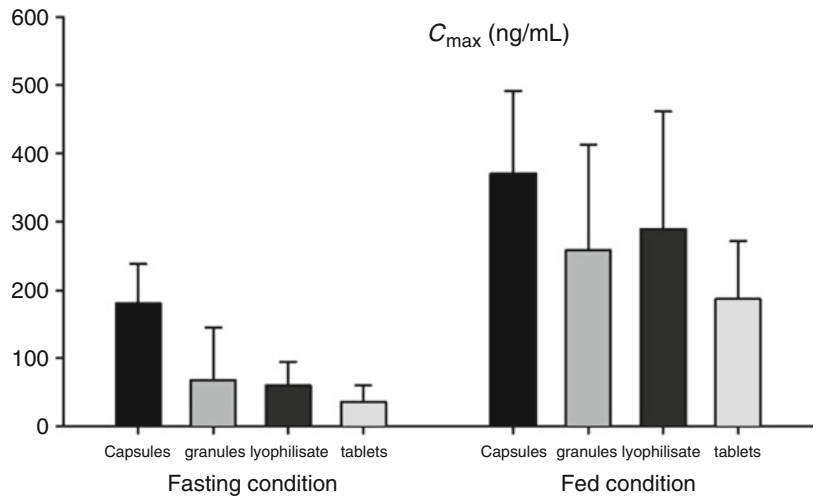

Fig. 1 Mean (SD) SAR001 C_{max} obtained after single oral administration to healthy young male subjects using four different formulations, in fasting or fed condition

Protocol Outline

Comparison of pharmacokinetics and safety of Modified Release formulations of 600 mg HMR456 with that of an immediate release formulation.

Primary Objective

To compare the PK characteristics of modified release (MR) formulations of HMR456 with the PK of an immediate release (IR) formulation of HMR456.

Secondary Objective

To assess the influence of food on the PK of MR formulations of HMR456.

Hypothetical in vivo dissolution was performed in addition to the objectives mentioned in the study protocol. Application of the method, results, and interpretation will be discussed here.

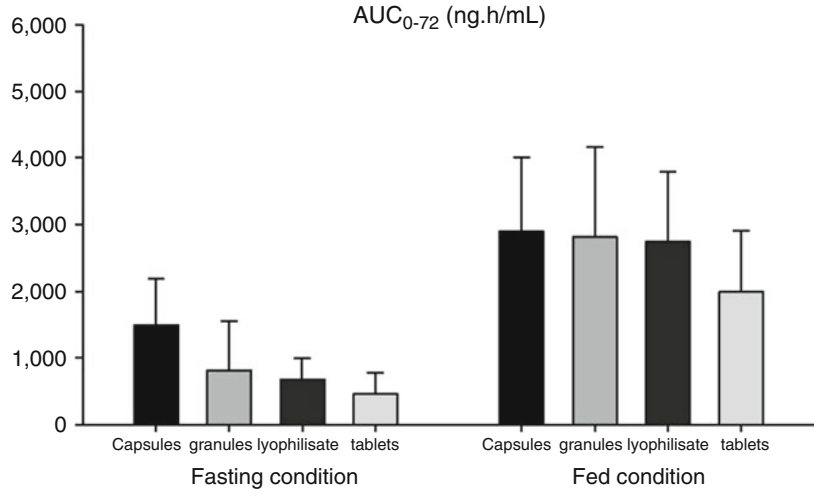

Fig. 2 Mean (SD) SAR001 AUC_{0-72} obtained after single oral administration to healthy young male subjects using four different formulations, in fasting or fed condition

Study Design

Single center, open-label, single-dose, four-period crossover study design with two parallel treatment groups.

Single oral doses of 600 mg HMR456 were given under fasting and under non-fasting conditions.

Inclusion Criteria

Healthy men aged 18–55 years.

Treatments

Treatment Group I

- Treatment A: 600 mg HMR456 (one film-coated tablet containing 200 mg + one film-coated tablet containing 400 mg given together) as IR formulation under non-fasting (NF) conditions (reference).
- Treatment B: 600 mg HMR456 in MR formulation (matrix tablet 1) under fasting (F) and NF conditions.
- Treatment C: 600 mg HMR456 in MR formulation (bilayer tablet 1) under F and NF conditions.

Treatment Group II

- Treatment A: 600 mg HMR456 (one film-coated tablet containing 200 mg + one film-coated tablet containing 400 mg given together) as IR formulation under non-fasting (NF) conditions (reference).
- Treatment D: 600 mg HMR456 in MR formulation (matrix tablet 2) under F and NF conditions.
- Treatment E: 600 mg HMR456 in MR formulation (bilayer tablet 2) under F and NF conditions.

MR tablet formulation 1 contains hydroxypropyl methyl cellulose, MR tablet formulation 2 contains carrageenan.

Pharmacokinetic Data

Concentration of HMR123 in plasma before and at predefined times after dosing.

Evaluation

Bioanalytical data: Individual plasma concentrations of HMR123 were tabulated together with standard descriptive statistics for each treatment. Individual and median profiles were presented graphically.

In vivo *dissolution data*: The individual hypothetical in vivo dissolutions for the four MR formulations administered under fasting and non-fasting conditions were estimated by numerical deconvolution using the individual response to the IR formulation given under non-fasting conditions as the weighting (impulse) function

using a hidden function of the validated HOEREP-PC software.

Plateau time data: The additional pharmacokinetic characteristics, i.e., plateau times (h) of HMR123 (time above 200, 500, 800, and 1,000 ng/mL) were calculated in the interval from administration ($t = 0$) to exactly 12 h thereafter from the plasma concentration–time data pairs and subjected to ANOVA. Points of intersection with a specific plateau concentration were obtained by linear interpolation.

PK data are presented elsewhere.

Critical Assessment of the Method

The study described here has a very complex design for its exploratory approach. It combines four different MR formulations, each tested under fasting and non-fasting conditions, and compares the results to the IR drug product as the reference formulation in two separate study groups. The bilayer tablets combine an IR component and an MR component in one vehicle. In this project, a close cooperation between the galenics department, analytical science department, and the clinical pharmacokinetic function (including study management, bioanalysis and PK evaluation) was mandatory. The in vitro/in vivo correlation was done by means of the deconvolution which is an appropriate surrogate to describe the in vivo dissolution.

The mismatch of surpassing 100% absorption of the active metabolite, that we observed in our study, is probably due to method constraints in combination with the immediate release data, as the deconvolution method requires data from a formulation with zero-order absorption for the impulse function, for example, an oral solution (oral bolus input); the immediate release formulation only provides an approximation to the required properties.

Modifications of the Method

The application of in vitro/in vivo correlation (IVIVC) and the tools for obtaining IVIVC including deconvolution are reviewed in FDA Guidance for Industry (1997).

References and Further Reading

FDA Guidance for Industry: Extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. September 1997

Example

To illustrate the amount of data that can be obtained using the deconvolution tool obtained from the study described above under "Procedure" is presented below.

Results – Hypothetical In Vivo Dissolution

Deconvolution is used to evaluate in vivo drug release and drug absorption from orally administered drug formulations (i.e., extended release) when data from a known drug input are available. The applied deconvolution method requires data from a formulation with zero-order absorption as known input, for example, an oral solution (oral bolus input); the immediate release formulation used as known input only provides an approximation to the required properties.

The medians and ranges of the hypothetical dissolution data for the active metabolite HMR123 obtained by deconvolution are listed in the following Table 3.

The following Figs. 3, 4, 5, 6, 7, 8, 9, and 10 show the hypothetical geometric mean in vivo dissolution profiles for the metabolite HMR123 (absolute amount absorbed vs. time as well as percentage of theoretical dose of the metabolite vs. time) (Table 4).

As can be seen in the above figures, as well as in Table 3, Treatments C and E (the bilayer tablets that contain the IR component) had a steeper amount absorbed profile as compared to the parallel matrix tablets (Treatments B and D). For example, the time for 50% of the maximal absorption looks much shorter (especially when Treatment C is compared to B). This effect was more pronounced under fasting conditions. Only with

Table 3 Hypothetical dissolution data for HMR123 obtained by deconvolution using Treatment A(NF) as impulse function. Median, range

Measures	B(NF)	B(F)	C(NF)	C(F)	D(NF)	D(F)	E(NF)	E(F)
Maximum amount absorbed (mg)	358.97	290.50	485.97	561.49	582.56	460.12	629.25	652.95
	239.61–727.06	173.93–484.88	287.67–994.55	300.14–1,817.29	465.29–1,076.11	339.60–795.42	430.72–5,674.72	452.19–3,183.05
Maximum amount absorbed[a] (% of dose)	63.22	51.16	85.58	98.88	102.59	81.03	110.82	114.99
	42.20–128.04	30.63–85.39	50.66–175.15	52.86–320.04	81.94–189.51	59.81–140.08	75.85–999.35	79.63–560.55
Time to reach maximum amount (h)	15.00	24.00	15.00	15.00	9.00	15.00	2.50	15.00
	4.00–24.00	15.00–24.00	6.00–15.03	0.50–36.00	2.00–24.00	10.00–24.00	0.50–24.00	0.50–15.00
Time to reach 20% of maximum amount (h)	1.81	0.55	0.57	0.27	0.76	0.34	0.51	0.26
	0.43–2.64	0.33–1.58	0.26–1.25	0.05–1.64	0.28–1.92	0.16–0.81	0.10–1.54	0.12–0.31
Time to reach 40% of maximum amount (h)	2.57	2.14	0.83	0.35	0.91	0.62	0.69	0.33
	0.97–3.38	0.54–5.47	0.33–1.73	0.11–1.97	0.36–2.62	0.31–1.16	0.20–1.83	0.24–0.81
Time to reach 50% of maximum amount (h)	2.80	3.34	0.91	0.40	1.04	0.69	0.81	0.37
	1.35–4.10	0.58–7.45	0.36–2.21	0.14–2.07	0.39–2.68	0.34–1.59	0.26–1.98	0.29–1.02
Time to reach 60% of maximum amount (h)	3.57	4.54	1.06	0.44	1.54	0.94	1.04	0.41
	1.51–6.00	0.62–9.33	0.40–3.19	0.16–2.25	0.43–2.75	0.37–2.22	0.30–2.13	0.33–1.22
Time to reach 80% of maximum amount (h)	5.27	6.95	2.95	1.64	1.79	2.54	1.44	0.48
	1.80–8.61	0.71–15.28	0.46–6.17	0.22–6.18	0.53–2.87	0.44–7.96	0.40–2.64	0.42–4.49

B(F/NF): 600 mg HMR456 in ER formulation (HPMC matrix tablet) under fasting (F) and non-fasting (NF) conditions, respectively
C(F/NF): 600 mg HMR456 in ER formulation (HPMC, bilayer tablet) under fasting (F) and non-fasting (NF) conditions, respectively
D(F/NF): 600 mg HMR456 in ER formulation (carrageenan matrix tablet) under fasting (F) and non-fasting (NF) conditions, respectively
E(F/NF): 600 mg HMR456 in ER formulation (carrageenan, bilayer tablet) under fasting (F) and non-fasting (NF) conditions, respectively
[a]Dose calculated for 567.84 mg HMR123 (corresponding to 600 mg HMR456)

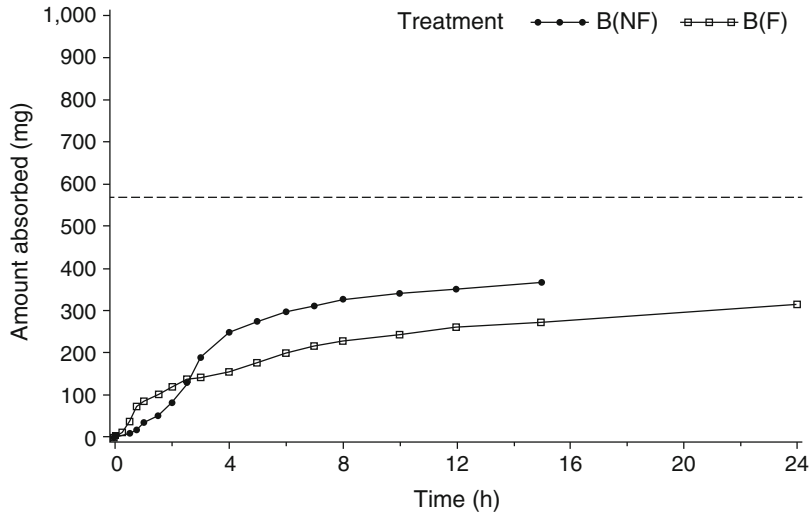

Fig. 3 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments B (F) and B(NF) (mg)

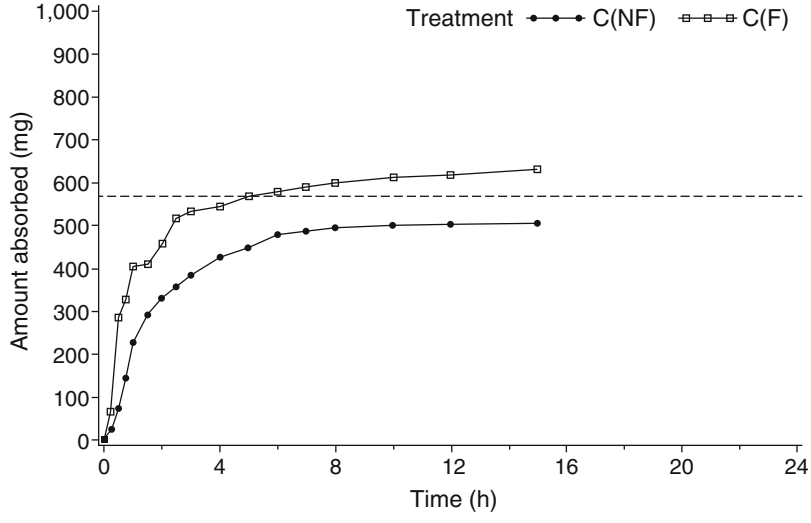

Fig. 4 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments C (F) and C(NF) (mg)

Treatment E (carrageenan bilayer tablets), the hypothetical in vivo dissolution profiles surpassed the 100% absorption, both under fasting and non-fasting conditions. For Treatment C, this occurred only under fasting conditions and for Treatment D only under nonfasting conditions.

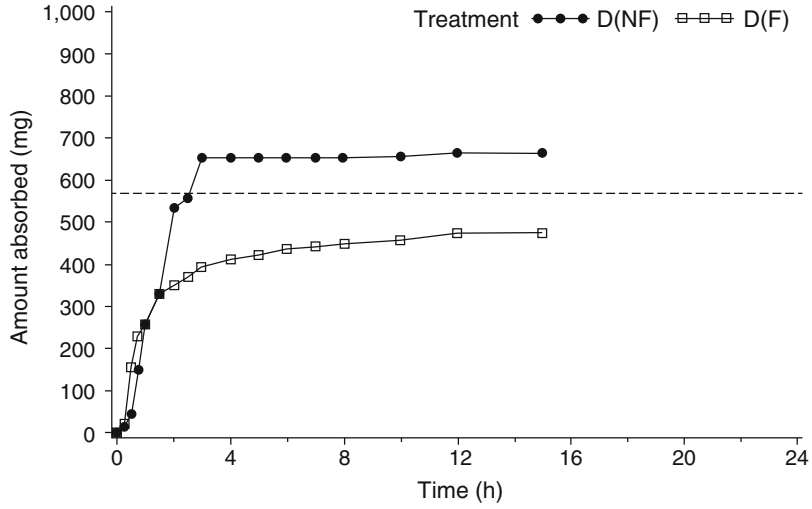

Fig. 5 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments D (F) and D(NF) (mg)

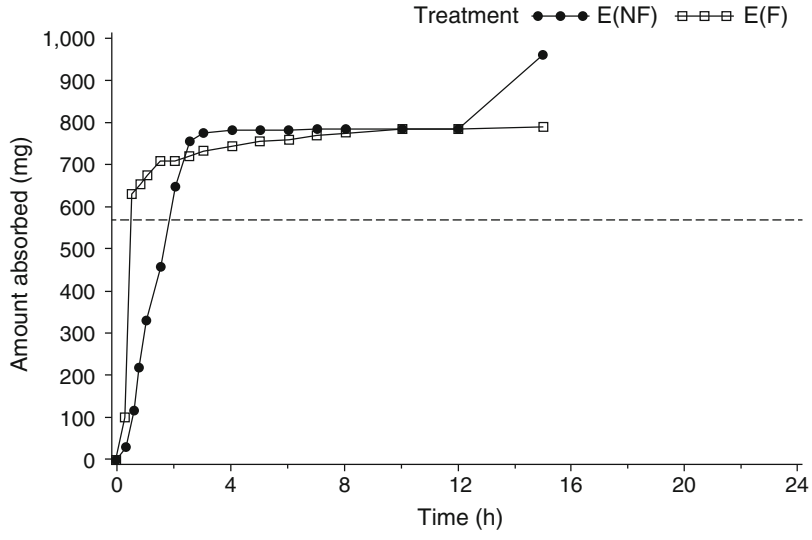

Fig. 6 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments E (F) and E(NF) (mg)

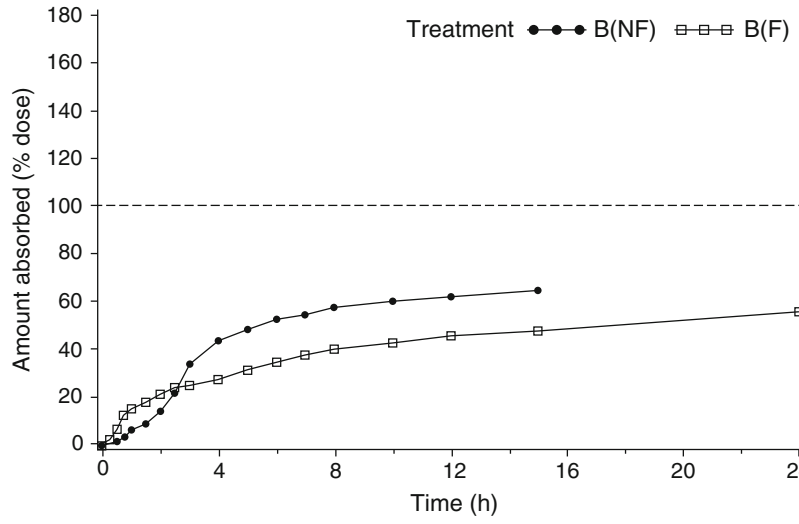

Fig. 7 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments B (F) and B(NF) (%dose)

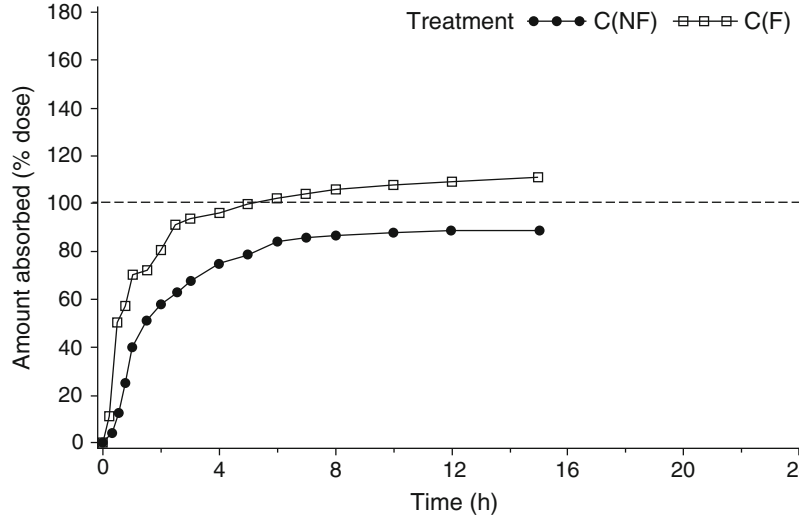

Fig. 8 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments C (F) and C(NF) (%dose)

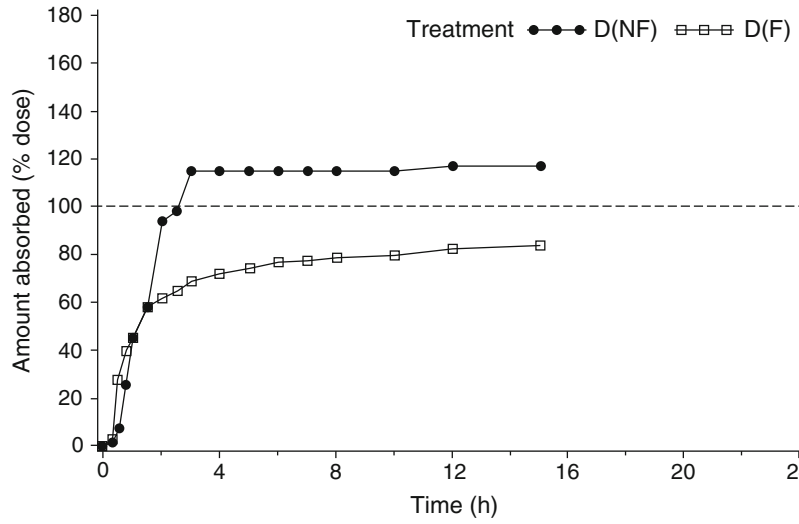

Fig. 9 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments D (F) and D(NF) (%dose)

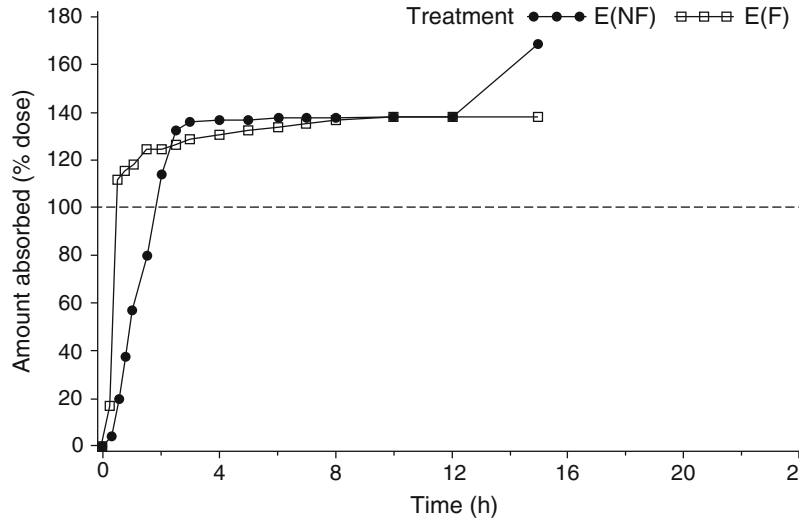

Fig. 10 Geometric means of the hypothetical in vivo dissolution profiles of HMR123. Treatments E (F) and E(NF) (%dose)

Table 4 Relative bioavailability estimates and 90% confidence intervals between formulations

Food condition	Parameter	Formulation comparison	Ratio estimate and 90% CI
Fasted	C_{max} (ng/mL)	Granule vs. capsule	0.30 (0.20, 0.45)
		Lyophilisate vs. capsule	0.29 (0.19, 0.43)
		Tablet vs. capsule	0.17 (0.11, 0.25)
	$AUC_{0–72}$ (ng·h/mL)	Granule vs. capsule	0.47 (0.34, 0.64)
		Lyophilisate vs. capsule	0.44 (0.32, 0.60)
		Tablet vs. capsule	0.29 (0.21, 0.39)
	$AUC_{0–168}$ (ng·h/mL)	Granule vs. capsule	0.50 (0.39, 0.63)
		Lyophilisate vs. capsule	0.52 (0.41, 0.67)
		Tablet vs. capsule	0.37 (0.29, 0.49)
Fed	C_{max} (ng/mL)	Granule vs. capsule	0.67 (0.51, 0.88)
		Lyophilisate vs. capsule	0.72 (0.54, 0.95)
		Tablet vs. capsule	0.47 (0.35, 0.62)
	$AUC_{0–72}$ (ng·h/mL)	Granule vs. capsule	0.95 (0.80, 1.12)
		Lyophilisate vs. capsule	0.94 (0.79, 1.11)
		Tablet vs. capsule	0.65 (0.54, 0.77)
	$AUC_{0–168}$ (ng·h/mL)	Granule vs. capsule	0.92 (0.79, 1.07)
		Lyophilisate vs. capsule	0.94 (0.81, 1.08)
		Tablet vs. capsule	0.70 (0.60, 0.81)

References and Further Reading

CPMP/EWP/560/95 Note for Guidance on the Investigation of Drug Interactions (CPMP, June 1998)

CPMP/EWP/QWP/1401/98 Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP, January 2002)

FDA Guidance for Industry: Extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations. September 1997

Guidance for Industry Scale-up and post-approval changes (SUPAC-IR): Chemistry, manufacturing, and control; in vitro dissolution testing and in vivo bioequivalence documentation. U.S. Department of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER). September 1995

Guidance for Industry Scale-up and post-approval changes (SUPAC-MR): Chemistry, manufacturing, and control; in vitro dissolution testing and in vivo bioequivalence documentation. U.S. Department of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER). September 1997

Guidance for Industry Statistical Approaches to Establishing Bioequivalence. U.S. Department of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER). January 2001

Guidance for Industry Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on the biopharmaceutics classification system (BCS). U.S. Department of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER). January 1999

Steinijans V-W, Hauschke D (1997) Individual bioequivalence. A European perspective. J Biopharm Stat 7 (1):31–34