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Approaches to conducting a physiologically relevant test (PRT) in the study of medicines containing substance IIc of the BCS subclass using sorafenib as an example

Alexandra V. Suvorova[1] ✉, Yuri V. Medvedev[1, 2], Polina A. Losenkova[1, 2], Olga S. Kramarenko[1], Eugenia A. Malashenko[2, 3], Andrey M. Poluyanov[1, 2], Igor E. Shohin[3]

[1] Limited Liability Company "Scientific Compliance". 1/2, 8, Simferopolsky bulvar, Moscow, 117246, Russia
[2] I. M. Sechenov First MSMU of the Ministry of Health of the Russian Federation (Sechenov University). 8/2, Trubetskaya str., Moscow, 119991, Russia
[3] Limited Liability Company "Center of Pharmaceutical Analytics" (LLC "CPHA"). 8, Simferopolsky bulvar, Moscow, 117246, Russia

✉ **Corresponding author:** Alexandra V. Suvorova. **E-mail:** info@scientific-compliance.ru

ORCID: Alexandra V. Suvorova – https://orcid.org/0000-0003-2611-501X;
Yuri V. Medvedev – https://orcid.org/0000-0001-6720-4954;
Polina A. Losenkova – https://orcid.org/0009-0005-2391-5267;
Olga S. Kramarenko – https://orcid.org/0009-0004-4406-1574;
Eugenia A. Malashenko – https://orcid.org/0000-0002-4183-7822;
Andrey M. Poluyanov – https://orcid.org/0000-0002-9960-6699;
Igor E. Shohin – https://orcid.org/0000-0002-1185-8630.

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Abstract

Introduction. Sorafenib is an antineoplastic drug belonging to class IIc according to the biopharmaceutical classification system (BCS) due to the presence of both acidic and basic properties. In addition to low solubility, sorafenib is characterized by high variability during clinical trials, in particular bioequivalence studies (BE). To selecting batches that can be recommended for BE studies, the dissolution kinetics test is currently widely used, however, the results of this test are not always sufficient and additional tests, for example, a physiologically relevant test, are advisable. To minimize the risks of obtaining nonequivalent results during the BE study, a physiologically relevant test (PRT) was carried out with further data processing and interpretation of the results of physiologically based pharmacokinetic modeling (PBPK).

Aim. The aim of the study is to conduct a physiologically relevant test (PRT) for the purpose of selecting a candidate batch for subsequent BE study of sorafenib drugs using the physiologically based pharmacokinetic model (PBPK).

Materials and methods. The objects of the study are Nexavar®, film-coated tablets, 200 mg (Bayer AG, Germany) (one batch) and Sorafenib, film-coated tablets, 200 mg (two batches) (Russia). The physiologically relevant test was performed on the SC PRT-6 device (LLC "Scientific Compliance", Russia). Quantitative analysis was performed by HPLC-UV on the Chromatec-Crystal HPLC 2014 device (JSC "Chromatec", Russia). The plasma concentration profiles were simulated using PK-Sim® software (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany).

Results and discussion. As part of the study, a method for the quantitative determination of sorafenib was developed and validated, a method for sample preparation was developed, and a method for conducting the PRT for sorafenib, as a representative of the IIc subclass of BCS, was developed. Based on the study results, release profiles were obtained that were used to select a candidate series for the BE study. The series were selected based on the PBPK analysis on a virtual population consisting of 36 healthy volunteers with activated enteropathic circulation, characteristic of sorafenib.

Conclusion. The PRT was carried out for the drug sorafenib. Quantitative determination was carried out by HPLC-UV according to the developed and validated method. The test resulted in obtaining data that were subjected to PBPK analysis. It was shown that the studied batches have high risks of non-equivalence during the bioequivalence study.

Keywords: sorafenib, HPLC, SC Powder, PBPK

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Yuri V. Medvedev participated in the development of the analytical method for the quantitative determination of sorafenib. Polina A. Losenkova was responsible for the analytical stage of the study. Alexandra V. Suvorova and Eugenia A. Malashenko performed statistical processing of the data. Andrey M. Poluyanov was responsible for the development and scientific justification of the experiment. Olga S. Kramarenko and Igor E. Shohin were responsible for the organizational part of the study. All the above-mentioned authors participated in the discussion of the obtained results in the form of a scientific discussion.

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Подходы к проведению физиологически релевантного теста (ФРТ) при изучении лекарственных препаратов, содержащих вещество подкласса IIc БКС, на примере сорафениба

А. В. Суворова[1]✉, Ю. В. Медведев[1, 2], П. А. Лосенкова[1, 2], О. С. Крамаренко[1], Е. А. Малашенко[2, 3], А. М. Полуянов[1, 2], И. Е. Шохин[3]

[1] Общество с ограниченной ответственностью «Сайнтифик Комплайнс». 117638, Россия, г. Москва, Симферопольский бульвар, д. 8., помещ. 1/2

[2] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И. М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет). 119991, Россия, г. Москва, ул. Трубецкая, д. 8, стр. 2

[3] Общество с ограниченной ответственностью «Центр фармацевтической аналитики» (ООО «ЦФА»). 117638, Россия, г. Москва, Симферопольский бульвар, д. 8

✉ **Контактное лицо:** Суворова Александра Вадимовна. **E-mail:** info@scientific-compliance.ru

ORCID: А. В. Суворова – https://orcid.org/0000-0003-2611-501X;
Ю. В. Медведев – https://orcid.org/0000-0001-6720-4954;
П. А. Лосенкова – https://orcid.org/0009-0005-2391-5267;
О. С. Крамаренко – https://orcid.org/0009-0004-4406-1574;
Е. А. Малашенко – https://orcid.org/0000-0002-4183-7822;
А. М. Полуянов – https://orcid.org/0000-0002-9960-6699;
И. Е. Шохин – https://orcid.org/0000-0002-1185-8630.

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Резюме

Введение. Сорафениб – противоопухолевое лекарственное средство, относящееся к классу IIc по биофармацевтической классификационной системе (БКС) за счет наличия и кислотных, и основных свойств. Кроме низкой растворимости, сорафениб характеризуется высокой вариабельностью при проведении клинических исследований, в частности исследований биоэквивалентности (БЭ). Для целей выбора серий, которые могут быть рекомендованы при проведении исследований БЭ, в настоящее время широко применяется тест кинетики растворения, однако результатов данного теста не всегда достаточно и проведение дополнительных тестов, например физиологически релевантного теста, является целесообразным. Для минимизации рисков получения неэквивалентных результатов при проведении исследования БЭ был проведен физиологически релевантный тест (ФРТ) с дальнейшей обработкой данных и интерпретацией результатов физиологически обоснованного фармакокинетического моделирования (ФОФМ).

Цель. Целью исследования является проведение физиологически релевантного теста (ФРТ) для целей выбора с применением ФОФМ (физиологически обоснованное фармакокинетическое моделирование, physiologically based pharmacokinetic model, PBPK) серии-кандидата для последующего исследования БЭ препаратов сорафениба.

Материалы и методы. Объектами исследования являются «Нексавар®, таблетки, покрытые пленочной оболочкой, 200 мг» (одна серия) (Bayer AG, Германия) и «Сорафениб, таблетки, покрытые пленочной оболочкой, 200 мг» (две серии) (Россия). Физиологически релевантный тест проводили на приборе СК ФРТ-6 (ООО «Сайнтифик Комплайнс», Россия). Количественный анализ проводили методом ВЭЖХ-УФ на приборе «Хроматэк-Кристалл ВЭЖХ 2014» (ЗАО СКБ «Хроматэк», Россия). Моделирование профилей «плазма – концентрация» проводилось с помощью программного обеспечения PK-Sim® (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Германия).

Результаты и обсуждение. В рамках выполнения исследований была разработана и валидирована методика количественного определения сорафениба, разработана методика пробоподготовки и методика проведения ФРТ для сорафениба как представителя подкласса IIc БКС. По результатам исследования получены профили высвобождения, которые были использованы для целей выбора серии кандидата для проведения исследования БЭ. Выбор серий

производился на основании ФОФМ-анализа на виртуальной популяции, состоящей из 36 здоровых добровольцев с активированной энтеропатической циркуляцией, характерной для сорафениба.
Заключение. Проведен ФРТ для препарата сорафениб. Количественное определение проводилось методом ВЭЖХ-УФ по разработанной и валидированной методике. В результате проведения теста были получены данные, подвергнутые ФОФМ-анализу. Было показано, что исследованные серии имеют высокие риски получения результатов с недоказанной эквивалентностью при проведении клинического исследования.

Ключевые слова: сорафениб, HPLC, SC Powder, ФОФМ

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Ю. В. Медведев принимал участие в разработке аналитической методики количественного определения сорафениба. П. А. Лосенкова отвечала за проведение аналитического этапа исследования. А. В. Суворова и Е. А. Малашенко проводили статистическую обработку данных. А. М. Полуянов отвечал за разработку и научное обоснование эксперимента. О. С. Крамаренко и И. Е. Шохин отвечали за организационную часть исследования. Все вышеуказанные авторы участвовали в обсуждении полученных результатов в форме научной дискуссии.

Для цитирования: Суворова А. В., Медведев Ю. В., Лосенкова П. А., Крамаренко О. С., Малашенко Е. А., Полуянов А. М., Шохин И. Е. Подходы к проведению физиологически релевантного теста (ФРТ) при изучении лекарственных препаратов, содержащих вещество подкласса IIc БКС, на примере сорафениба. *Разработка и регистрация лекарственных средств.* 2024;13(3):176–185. https://doi.org/10.33380/2305-2066-2024-13-3-1900

INTRODUCTION

Pharmaceutical research is an important stage of the preparation of a medicinal product for bioequivalence study with the aim of its state registration. After the finished drug form is obtained, the developers face an important challenge of choosing the batch of the drug to be compared with the reference drug. There are a variety of ways of reducing the risk of obtaining non-equivalent results, one of which is conducting a dissolution kinetics comparison test (DKCT) in dissolution media simulating the conditions of various sections of the gastrointestinal tract (GIT). Possession of the results of such test, knowledge of the BCS Class of the active pharmaceutical ingredient (API) under study, and consideration of its biopharmaceutical properties allow improving the accuracy of selection of the batch to undergo the bioequivalence studies [1–3].

With a view to collecting additional information, other methods besides DKCT are developed and introduced into the field of pharmaceutical analysis, e.g. GISS (gastro intestinal simulation system), TIM (TNO Gastro-Intestinal Model), computer simulation [4]. These methods allow modeling the behavior of drugs within GIT under different conditions; for example, the function of physiological transit from one GIT section to another is added; bile secretion and food intake are taken into account, and much more [5–10]. The physiologically relevant test (PRT) is the next stage of *in vitro* studies providing additional information about the API being studied before conducting the bioequivalence tests. PRT is particularly useful for highly variable API and for API related to BCS class II and, in some degree, into Class IV. During PRT, disintegration and release of API occur with further transit to subsequent sections of the GIT model.

An important feature of PRT is the application of media that are more similar to the physiological fluids than the media being considered "mandatory" for DKCT according to applicable legislation (pH 1.2 hydrochloric acid solution, pH 4.5 and 6.8 buffer solutions) [11, 12].

It is recommended to use biorelevant media in PRT, such as Fasted State Simulated Gastric Fluid (FaSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF), Fed State Simulated Intestinal Fluid (FeSSIF) containing either sodium taurocholate and lecithin or various combinations with surfactants [13–16]. Performing PRT in biorelevant media yields results which, being combined with various kinds of mathematical modeling, such as physiologically based pharmacokinetic (PBPK) modeling, allow the characterization of pharmacokinetics of substances on the basis of their physicochemical properties and physiology of humans or animals [17–19].

Physiologically relevant testing is most appropriate for poorly soluble substances, one of which is Sorafenib having log P = 3.8 [20]. Sorafenib belongs to BCS Class II and due to its both acidic and basic properties falls into Subclass "c" [21, 22]. Due to its polymorphism [23], Sorafenib is characterized by high variability, which makes this substance an interesting object for PRT being conducted for the purpose of pharmaceutical research and subsequent PBPK modeling study.

The structural formula of Sorafenib is shown in Figure 1.

MATERIALS AND METHODS

Objects of study

The objects of study were as follows: "Nexavar® film-coated tablets, 200 mg" (Bayer AG, Germany) (one batch), and "Sorafenib film-coated tablets, 200 mg" (Russia) (two batches); all the drugs under investigation were valid for the date of testing.

Reagents and solutions

The following reagents were used in the study: purified water type I; concentrated hydrochloric acid (class "extra pure", "Component-Reaktiv" LLC, Russia); concentrated orthophosphoric acid (class "Food and pharma grade", NeoFroxx GmbH, Germany); sodium hydroxide (class "p.a.", "Component-Reaktiv" LLC, Russia); sodium dihydrogen phosphate (class "extra pure", "Component-Reaktiv" LLC, Russia); sodium chloride (class "extra pure", "Component-Reaktiv" LLC, Russia); SC Powder (produced by "Scientific Compliance" LLC, Russia); acetonitrile (class "HPLC gradient grade", produced by Alpha Chemika, India).

Equipment and software

The physiologically relevant test was conducted on an SC PRT-6 unit ("Scientific Compliance" LLC, Russia). Chromatographic separation was carried out on a high-efficient liquid chromatograph "Khromatek-Kristall HPLC 2014" (SKB "Khromatek" JSC, Russia) equipped with a column thermostat, degasser, automatic sampler, and a UV detector. Raw data processing was performed with the use of the "Khromatek-Analytic" v. 214.00045.51 software.

Modeling of the plasma concentration-time profiles was carried out with the "PK-Sim®" software (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany).

Chromatography conditions

The chromatographic separation was carried out using a GL Sciences InertSustain C18 chromatography column, 4.6 × 100 mm, 5 µm, in gradient separation mode. Mobile phase A was presented by 0.2 % formic acid solution, phase B – by acetonitrile. Flow rate: 0.8 l/min; column temperature: 40 °C. Detection was performed at a wavelength of 262 nm; the injected volume of sample was 5 µl. Analysis run time per sample was 6.1 minutes.

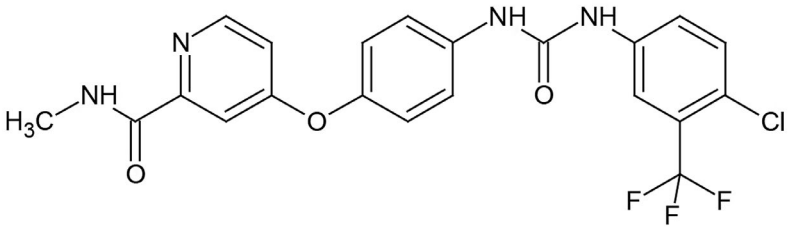

Figure 1. Chemical structure of sorafenib

RESULTS AND DISCUSSION

Elaboration of the PRT procedure

According to the FDA Dissolution Database, Sorafenib as a BCS Class II drug substance is dissolved in 0.1 M solution of hydrochloric acid in the presence of sodium lauryl sulfate. Based on the properties of Sorafenib and information on its pharmacokinetics, it was considered practical to perform its PRT according to a modified procedure, where the stomach would be presented by the second section of the test model into which the drug would be placed.

The PRT was conducted using a type II paddle stirrer equipped with a modified paddle with two round holes, rotating at 25 rpm and periodically accelerating up to 180 rpm. One tablet of the drug being studied was placed into each vessel simulating the stomach (the second section of the test apparatus). Then the paddle was lowered into the dissolution vessels. The initial volume of the dissolution medium in the first and third vessels was 0 ml, and 300 ml of FaSSGF medium mixed with purified water was in the second vessel. All the vessels were pre-heated at 37 ± 0.5 °C under thermostatic control before launching the test.

PRT process arrangement

The first section of the apparatus simulated the stomach conditions after the drug has been transferred further into subsequent sections of the GIT. This section was not filled initially, and was filled later in process of the test by way of transit of the gastric juice back from the second section according to the equation of first order kinetics. By the 40th minute, the volume of content of the first section reached 250 ml and was kept constant till the end of the study.

In the beginning of the test the second section represented the stomach, and later the duodenum, simulating API transit along the GIT. The transit mechanism was implemented as follows: first, API in a mixture of 50 ml of FaSSGF and 250 ml of water (a glass of water used to wash down a tablet) was placed into the second vessel; pH value of this mixture was about 2.84 (these starting conditions simulated the stomach in fasted state after taking the drug). Then this vessel was drained into the first vessel according to the equation of first order kinetics. The emptying time (down to residual volume of 50 ml) was 40 minutes. From the 40th to 55th minute, FaSSIF (Fasted State Simulated Intestinal Fluid) dissolution medium was being secreted into the second section until the volume reached 75 ml, which simulated the API transit from the stomach into the duodenum. This value of the section volume remained constant throughout the test.

The third section of the apparatus simulated the intestine and served for collecting the secretion from the second section. The volume of fluid in this section increased from the 40th minute to the end of the test due to the transfer of content of the second section. The initial volume in this section was 0 ml.

Over the specified time intervals, 1.0 ml samples of the medium were automatically withdrawn from the appropriate sections. After the sampling, the necessary sample preparation was performed, and the amount of dissolved Sorafenib was determined by HPLC-UV method. The physiologically relevant testing of the drugs under investigation and the reference drug were conducted in parallel, on 6 units of each drug.

Elaboration of the procedure for sample preparation within the scope of PRT

The modified (hybrid) scheme of conducting PRT testing of poorly soluble drugs is characterized by the presence of large numbers of suspended particles in the samples. Another particular feature of such samples is that the resulting solution becomes saturated, and in the process of cooling in the automatic sampler tray the solubility of the substance may decrease, which would be accompanied by reduction in concentration. In order to prevent the solution concentration from changing and avoid obtaining unreliable data, the following sampling procedure was elaborated: after the sample has been taken, the aliquot was settled until suspension was dropped down completely; then 750 µl of the supernatant fluid was carefully drawn out and added with 750 µl of acetonitrile, thoroughly stirred, and the solution thus obtained was filtered through syringe filters into the chromatography vials.

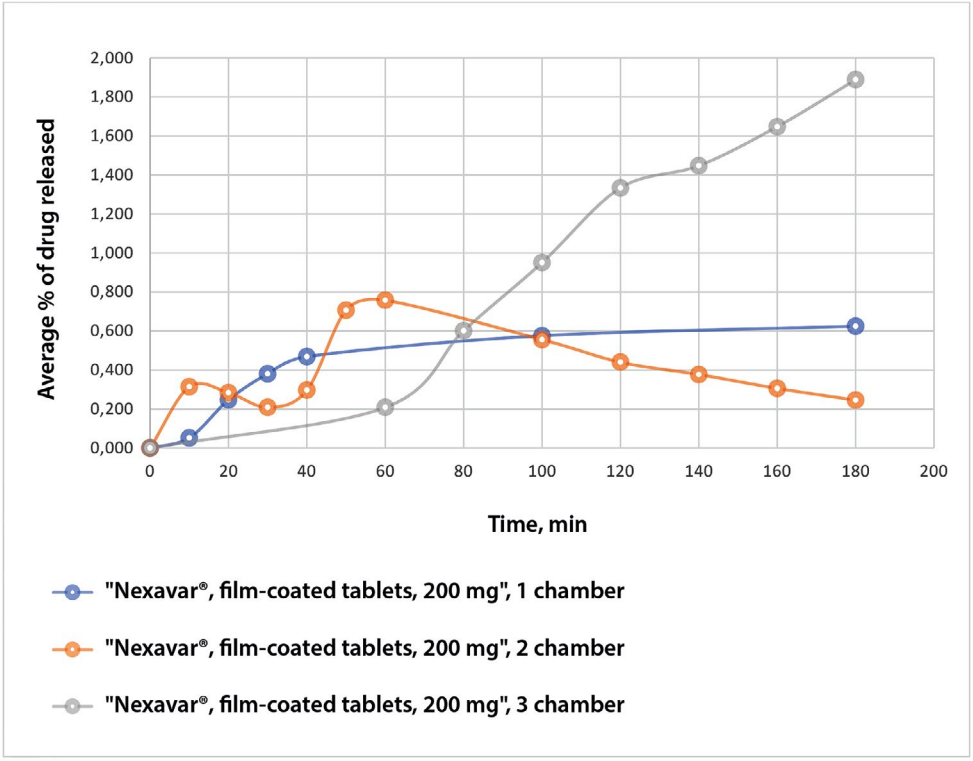

Figure 2. Average dissolution profiles of sorafenib in the medicinal product «Nexavar®, film-coated tablets, 200 mg», in three chambers of the apparatus

Elaboration of the procedure for quantitative determination of Sorafenib content in samples obtained in the PRT

A physiologically relevant test is performed in relatively small volumes of dissolution media. Being a poorly soluble substance, Sorafenib in PRT conditions forms low-concentration solutions, which makes it necessary to develop and validate a procedure for quantifying the active substance in ranges significantly differing from those to which other quantitative methods apply, like, for instance, in case of dissolution kinetics comparison tests (DKCT).

The procedure was validated by the following parameters: specificity, linearity (calibration curve), trueness and repeatability within one analytical cycle, intermediate trueness and precision, standard solutions stability, samples stability during the PRT, and samples 24 hours stability in dissolution media.

Linearity was evaluated at 7 levels in the range from 1.00 to 20.00 μg/ml; evaluation of accuracy, precision, and stability of various kinds was performed at 4 levels in the same range.

The procedure validation tests showed satisfactory results.

Results of the performed PRT

Based on the data obtained, averaged diagrams "drug release percentage – time" were plotted (Figures 2-4).

The results of the test showed a partial release of all drugs under physiologically relevant conditions, however, the data obtained allows comparison for assessing the similarity of different batches of the studied drug to the reference one and may be used for further accomplishment of predictive tasks, e.g. physiologically based pharmacokinetic (PBPK) modeling.

Results of the performed PBPK modeling

The model describing Sorafenib was developed with the use of the PK-Sim® software (Systems Biology Software Suite 11.2, Bayer Technology Services GmbH, Germany).

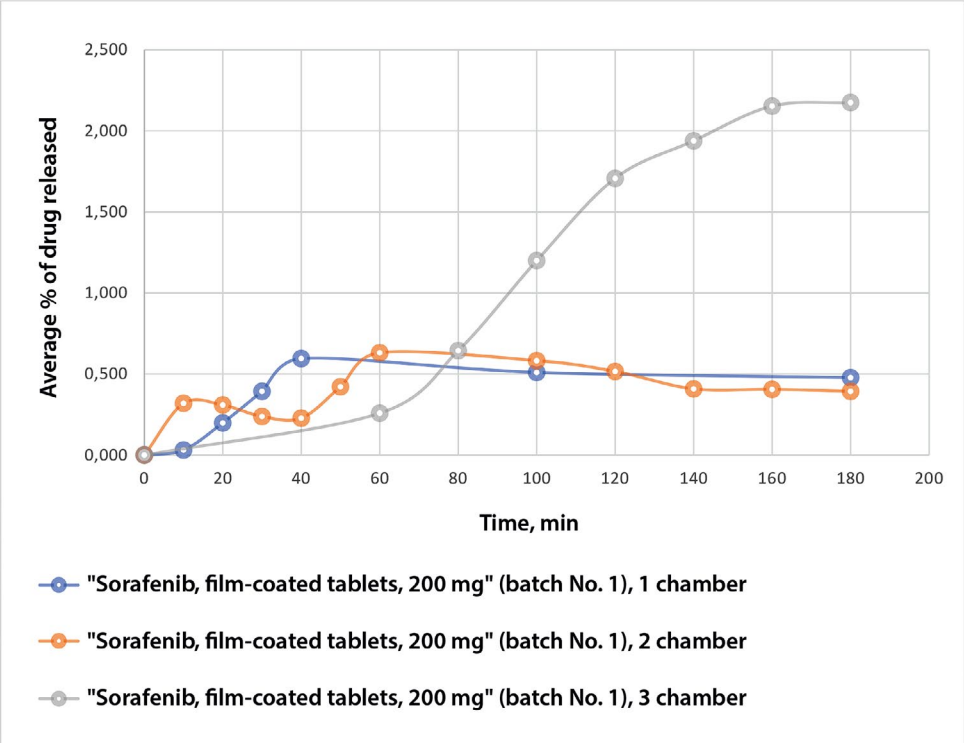

Figure 3. **Average dissolution profiles of sorafenib in the medicinal product «Sorafenib, film-coated tablets, 200 mg», batch No. 1 in three chambers of the apparatus**

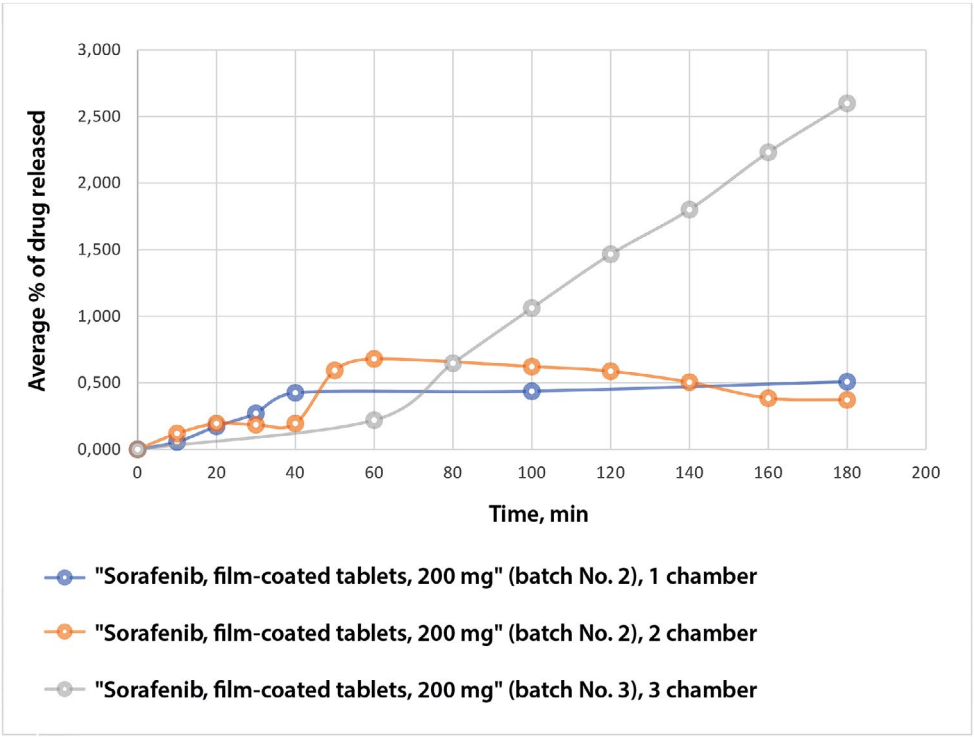

Figure 4. **Average dissolution profiles of sorafenib in the medicinal product «Sorafenib, film-coated tablets, 200 mg», batch No. 2 in three chambers of the apparatus**

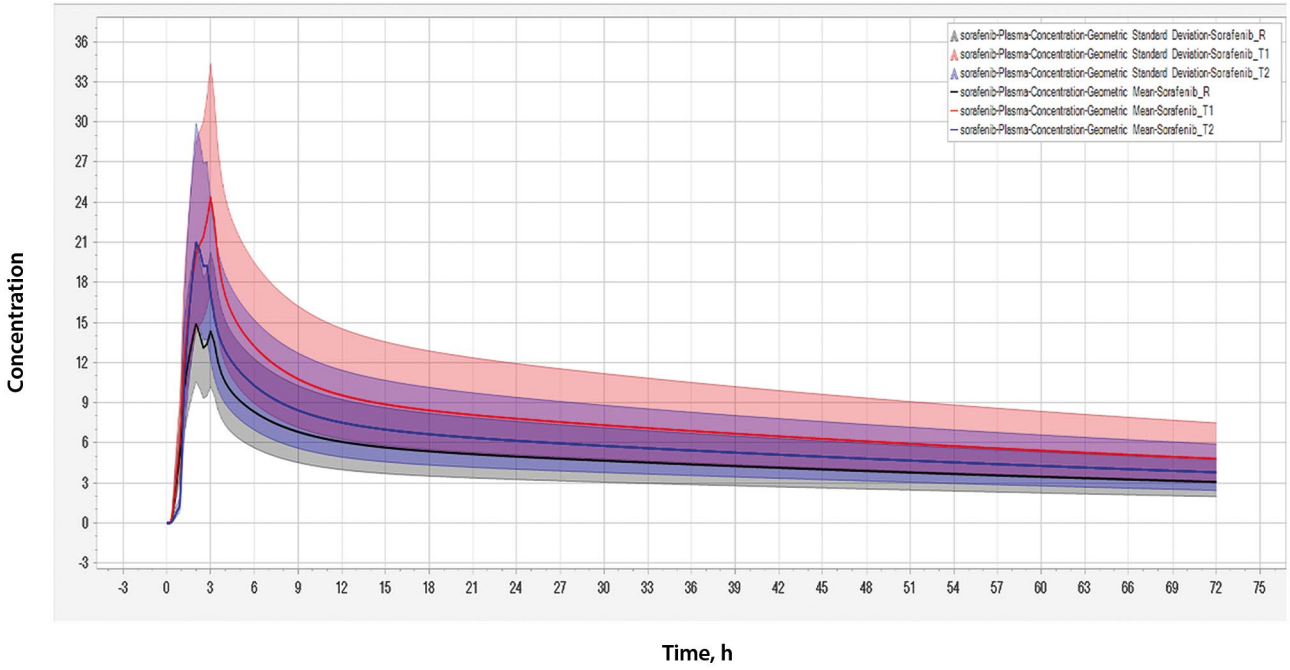

Figure 5. Simulated concentration-time profile for all tested drugs. The solid line shows the geometric mean concentrations for each drug, and the colored area shows the standard deviations for the geometric mean concentrations for each drug

The virtual population was chosen based on data from a clinical study[1]. The virtual population consisted of 36 healthy volunteers, white, aged 18 to 65, with body mass index from 18.5 to 30 kg/m^2, minimum weight for men – 50.0 kg, for women – 45.0 kg. For the evaluation of profiles regardless of gender, the number of female and male individuals was selected equal. All the people in the population had the enterohepatic circulation active, which ensured a continuous excretion of bile into the duodenum.

The model described the following design of the study: a single dose administration of film-coated tablets containing 200 mg of the active substance Sorafenib.

With the help of the model developed, the virtual population pharmacokinetic profiles of the drugs being studied were plotted, based on integrated data on the drug release in the second and third sections obtained *in vitro* for two batches of the preparation under test and one batch of the reference preparation. The ratios T1/R and T2/R for the key pharmacokinetic parameters are presented in Table 1; the generated profiles are shown in Figure 5.

[1] Bioequivalence Study of Sorafenib Tablet and Nexavar. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT02599337. Accessed: 01.08.2024.

Table 1. Predicted relationships for key pharmacokinetic parameters

Parameter	RATIO T1/R, %	RATIO T2/R, %
AUC_{0-inf}	156.60	123.60
AUC_{0-72}	156.40	123.60
C_{max}	163.70	140.70

Relying on the obtained concentration-time profiles and ratios of geometric mean values for pharmacokinetic parameters AUC_{0-inf}, AUC_{0-72}, C_{max}, it was shown that the risk of getting results with unproven bioequivalence is high for both batches of the drug being tested.

CONCLUSION

In the present study, a procedure for quantitative determination of Sorafenib content in samples obtained from PRT testing of Sorafenib based drugs was developed and validated. A procedure for PRT of a drug with BCS Subclass IIc active substance – Sorafe-

nib was developed and approved. Based on the test results, the profiles of dissolution of Sorafenib were obtained which were used in the pharmaceutical research aiming at selecting the batch for bioequivalence study.

Within the scope of this work, a physiologically based pharmacokinetic modeling of the studied drugs behavior in a virtual population was carried out, showing that the risk of getting results with unproven bioequivalence is high, and that the tested batches of the drugs cannot be recommended for use in bioequivalence testing.

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