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A biorelevant test for tablets glycine sublingual in the "simulated saliva" dissolution medium

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Abstract

Introduction. Biorelevant dissolution media reconstitute the composition of the contents of the gastrointestinal tract. They are used as dissolution media in the evaluation of dissolution profiles of different dosage forms. Simulated biological fluids allow prediction of *in vivo* test results. The development of the composition of simulated salivary fluid allows the evaluation of drug properties under physiologically relevant conditions.

Aim. Evaluation of the release of the drug product "glycine, sublingual tablets, 100 mg", domestically produced in Simulated Saliva 5 pH 6.8.

Materials and methods. The preparations used for analysis were: «Glycine, sublingual tablets, 100 mg», domestically produced with valid expiration date. Comparative dissolution kinetics test was carried out on the dissolution test apparatus DT 6 (ERWEKA GmbH, Germany). Chromatographic separation and detection were performed on a Waters W1525 Binary HPLC Pump high-performance liquid chromatograph (Waters Corporation, USA) equipped with column and sample thermostat, degasser, autosampler and Waters 2487 Dual Absorbance Detector (Waters Corporation, USA). Detection was performed at a wavelength of 254 ± 2 nm after derivatization of the glycine molecule with 4-toluenesulfonyl chloride. A Grace Platinum C18-EPS 5 μm 4.6 × 250 mm Grace Platinum C18-EPS 5 μm 4.6 × 250 mm column (Grace, USA) and a Grace Platinum C18-EPS 5 μm 4.6 × 250 mm pre-column (Grace, USA) were used. Microsoft Excel software was used for drug release calculations.

Results and discussion. The technique for quantitative determination of glycine was developed and validated under DKCT in purified water medium and Simulated Saliva 5 pH 6.8. The validated analytical range of the methodology was 10–110 % of the nominal concentration of the dosage form in 300 mL volume of medium. The developed analytical technique was validated in the biopredictive *in vitro* test of glycine preparations. During the study in Simulated Saliva medium for drug formulations, more discriminative data were obtained, which were expressed as: different dissolution rate, curvature of the slope of the dissolution profile and time to reach the plateau in comparison with the dissolution medium purified water.

Conclusion. The quantification technique was developed and validated for biopredictive tests of tablets "Glycine, sublingual tablets, 100 mg". The analytical range of the technique was 10–110 % of the nominal concentration of the dosage form in 300 mL volume of medium. The results of the test in artificial saliva medium were more discriminatory.

Keywords: test comparative dissolution kinetics, glycine, Simulated Saliva

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. Sofya D. Kulikova, Zhanna M. Kozlova, Andrey M. Poluyanov invented and designed the experiment. Sofya D. Kulikova, Polina A. Losenkova and Maria B. Sokol analyze on HPLC-UV. Sofya D. Kulikova and Polina A. Losenkova and Maria B. Sokol performed a comparative dissolution kinetics test. Sofya D. Kulikova and Polina Ya. Parshinova participated in data processing. Sofya D. Kulikova, Zhanna M. Kozlova, Andrey M. Poluyanov participated in writing the text of the article. Andrey M. Poluyanov was the leader of this study. All authors participated in discussion of the results.

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Биорелевантный тест для таблеток подъязычных с глицином в среде растворения «искусственная слюна»

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Резюме

Введение. Биорелевантные среды растворения воссоздают состав содержимого желудочно-кишечного тракта. Они используются в качестве среды растворения при оценке профилей растворения различных лекарственных форм. Имитированные биологические жидкости позволяют прогнозировать результаты испытаний *in vivo*. Разработка состава имитированной слюнной жидкости позволяет оценить свойства лекарственного препарата в физиологически релевантных условиях.

Цель. Оценка высвобождения лекарственного препарата «глицин, таблетки подъязычные, 100 мг» отечественного производства в среду растворения Simulated Saliva 5, pH 6,8.

Материалы и методы. Для анализа использовались препараты: «Глицин, таблетки подъязычные, 100 мг» отечественного производства с действующим сроком годности. Тест сравнительной кинетики растворения проводили на приборе для теста «Растворение» DT 6 (ERWEKA GmbH, Германия). Хроматографическое разделение и детектирование проводили на высокоэффективном жидкостном хроматографе Waters W1525 Binary HPLC Pump (Waters Corporation, США), оснащенном термостатом колонок и образцов, дегазатором, автосамплером и ультрафиолетовым детектором Waters 2487 Dual Absorbance Detector (Waters Corporation, США). Детектирование проводилось при длине волны 254 ± 2 нм после дериватизации молекулы глицина 4-толуолсульфонилхлоридом. Использовали колонку Grace Platinum C18-EPS, 4,6 × 250 мм, 5 мкм (Grace, США) и предколонку Grace Platinum C18-EPS, 4,6 × 250 мм, 5 мкм (Grace, США). Для исследования использовалось следующее программное обеспечение: валидированная автоматическая таблица Microsoft Excel для расчета значений высвобождения глицина.

Результаты и обсуждение. Разработана и валидирована методика количественного определения глицина в рамках ТСКР в среде воды очищенной и среде, имитирующей слюну человека, Simulated Saliva 5, pH 6,8. Подтвержденный аналитический диапазон методики составил 10–110 % от номинальной концентрации лекарственной формы в объеме среды 300 мл. Разработанная аналитическая методика была апробирована в ходе проведения биопредиктивного *in vitro* теста препаратов глицина. При проведении исследования в среде Simulated Saliva для лекарственных препаратов были получены более дискриминативные данные по сравнению со средой растворения «вода очищенная», что выражалось в разной скорости растворения, кривизне наклона профиля растворения и времени выхода на плато.

Заключение. Разработана и валидирована методика количественного определения для проведения биопредиктивных тестов таблеток «Глицин, таблетки подъязычные, 100 мг». Аналитический диапазон методики составил 10–110 % от номинальной концентрации лекарственной формы в объеме среды 300 мл. Результаты проведения теста в среде искусственной слюны обладали большей дискриминативностью в сравнении с водой очищенной и позволили обнаружить различия в полноте высвобождения лекарственных препаратов, времени достижения плато и угла наклона кривой профиля растворения.

Ключевые слова: тест сравнительной кинетики растворения, глицин, Simulated Saliva

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

Вклад авторов. С. Д. Куликова, Ж. М. Козлова, А. М. Полуянов придумали и разработали эксперимент. С. Д. Куликова, П. А. Лосенкова и М. Б. Сокол провели исследование методом ВЭЖХ-УФ и тест сравнительной кинетики растворения. С. Д. Куликова, и П. Я. Паршинова участвовали в обработке данных. С. Д. Куликова, Ж. М. Козлова, А. М. Полуянов участвовали в написании текста статьи. А. М. Полуянов был руководителем данного исследования. В обсуждении результатов участвовали все авторы.

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INTRODUCTION

Biorelevant dissolution media are artificial media simulating the human gastrointestinal fluids in terms of their composition and such properties as: pH, osmolality, viscosity, buffer capacity, and surface tension [1–3]. *In vitro* testing with biorelevant dissolution media can allow predicting the results to be obtained *in vivo* [4].

In current pharmaceutical research, there is a separate methodology related to the dissolution media simulating the conditions of the oral cavity [5]. In order to better simulate the human saliva, these media must have the pH value close to the physiological pH [6]. The pH of human saliva varies between 6.4 and 7.4, depending on factors such as diet, secretion rate, and oral hygiene [7, 8]. It is worth mentioning that this pH can also be affected by drinking beverages with a pH other than neutral, such as, for instance, coffee which reduces the pH value [9].

Biorelevant dissolution media differ in buffer capacity and acidity and are used for different purposes, as appropriate [10, 11]. Types and specific features of the biorelevant oral media are shown in Table 1. For the purposes of solid dosage forms studies formulation 5 is suitable as it was specially developed for prediction of oral drug release profiles.

The most common components in creating a medium that mimics the human saliva are: salts such as chlorides, carbonates and phosphates necessary to maintain optimal pH, osmotic and ionic strength; proteins such as amylase and mucin also necessary to replicate the conditions of the human oral cavity [10]. The physiological amount of saliva that the average person produces during a day is between 1–2 liters [12]. In the present experiment, this volume was reduced to a more physiologically relevant value of 300 ml, which is also the minimum allowable volume for the ERWEKA DT 6 Series Dissolution Tester (ERWEKA GmbH, Germany).

These media are of particular importance with regard to sublingual and buccal drugs testing [13, 14]. The sublingual and buccal routes of administration are used to achieve a systemic effect and have shown to be an effective alternative to the conventional oral route [15]. Among the advantages of the buccal and sublingual forms of the medication, we can distinguish rapid onset of action of the drug and the absence of hepatic first-pass effect [16].

Table 1. **Types and characteristics of biorelevant oral dissolution media**

Biorelevant dissolution medium Simulated Saliva (SS)	Characteristics	Composition, g
SS 1	Was developed to study the corrosion behavior of all metallic materials in dentistry	potassium chloride – 0.720 calcium chloride dihydrate – 0.220 sodium chloride – 0.600 potassium phosphate – 0.680 sodium phosphate – 0.866 potassium bicarbonate – 1.500 potassium thiocyanate – 0.060 citric acid – 0.030 pH 6.5
SS 2	Was developed to predict localized oral exposure to carcinogenic compounds in tobacco smoke	potassium chloride – 0.720 calcium chloride dihydrate – 0.220 sodium chloride – 0.600 potassium phosphate – 0.680 sodium phosphate – 0.866 potassium bicarbonate – 1.500 potassium thiocyanate – 0.060 citric acid – 0.030 pH 7.4
SS 3	Was used to predict outcomes in a study of mouthwashes	calcium chloride dihydrate – 0.228 sodium chloride – 1.017 sodium phosphate – 0.204 magnesium chloride hexahydrate – 0.061 potassium carbonate hemihydrate – 0.603 sodium phosphate monohydrate – 0.273 submandibular mucin – 1.000 alpha-amylase – 2.000
SS 4	Was developed to study interactions between drug molecules and the oral mucosa	potassium chloride – 0.149 sodium chloride – 0.117 sodium bicarbonate – 2.100 alpha-amylase – 2.000 gastric mucin – 1.000
SS 5	Was developed to monitor the release of oral fast-dissolving drugs	sodium chloride – 8.00 potassium phosphate – 0.19 sodium phosphate – 2.38 pH 6.8

MATERIALS AND METHODS

Reagents and solutions

The reagents used in the test were as follows: purified water, type I; concentrated hydrochloric acid (HCl), class "extra pure" ("Sigma Tec" LLC, Russia); glacial acetic acid (CH_3COOH), class "RFE, USP, BP, Ph. Eur." (PanReac AppliChem, USA); concentrated orthophosphoric acid (H_3PO_4), class "for HPLC" (Scharlau, Spain); sodium hydroxide (NaOH), class "p.a." ("Component-Reaktiv" LLC, Russia); dipotassium phosphate (K_2HPO_4), class "p.a." ("LenReactiv" JSC, Russia); sodium dihydrogen phosphate (NaH_2PO_4), class "p.a." ("LenReactiv" JSC, Russia); disodium hydrogen phosphate (Na_2HPO_4), class "pure EP" (NeoFroxx GmbH, Germany); acetonitrile (ACN), class "for UHPLC" (PanReac AppliChem, USA); p-toluenesulfonyl chloride (TsCl) (Merck KGaA, Germany); boric acid, class "extra pure" ("LenReactiv" JSC, Russia).

The study was carried out on three lots of the drug "Glycine, sublingual tablets, 100 mg" (non-expired, produced by a domestic manufacturer). The auxiliary ingredients for preparation of solution were provided by the manufacturer of the tablets.

As the reference sample, a standard powdery substance with a purity of 98.5 % was used (series 016022023, non-expired, produced by a domestic manufacturer).

As the quality control medium, purified water was used.

Procedure of preparation of the medium simulating the human saliva – Simulated Saliva type 5, pH 6.8

Sodium chloride in the amount of 8 g was added into a 1000 ml graduated flask and dissolved in 200 ml of purified water. The solution obtained was added with 0.19 g of potassium hydroorthophosphate and 2.38 g of sodium dihydrophosphate; then the volume of solution was brought to the mark with purified water and thoroughly stirred. The pH of the solution was measured with a pH meter and raised to 6.8 as necessary with either 1 M sodium hydroxide solution or 42.5 % orthophosphoric acid [10].

All thus obtained dissolution media were then filtered by a vacuum filtration system and degassed with the use of a vacuum pump.

Test equipment

The dissolution kinetics comparison test (DKCT) was conducted on a DT 6 Dissolution Tester (ERWEKA GmbH, Germany) with a paddle stirrer rotating at 50 rpm, at a temperature of 37 ± 0.5 °C. The volume of purified water dissolution medium was 1000 ml. The volume of Simulated Saliva 5 dissolution medium with pH 6,8 was 300 ml. The sampling was performed at time points 5, 10, 15, 20, and 30 min. The quantitative content of the released Glycine was determined by HPLC-UV method.

Chromatographic separation and detection of the substance were carried out using a HPLC system consisting of Waters W1525 Binary HPLC pump (Waters Corporation, USA), Waters 2487 Dual Absorbance UV/Vis Detector (Waters Corporation, USA), and Grace Platinum C18-EPS Chromatography Column, 4,6 × 250 mm, 5 µm (Grace, USA).

Data processing and calculations were performed with the use of validated software running on the Waters W1525 Binary HPLC pump with an UV Detector (Waters Corporation, USA).

Chromatographic separation and detection procedures were taken from scientific sources and refined to the requirements of the experiment [17].

RESULTS AND DISCUSSION

Quantitative analysis procedure validation

For the purposes of the study, a procedure of Glycine quantitative content determination allowing to estimate the percentage of release from solid dosage form into media simulating the human saliva was developed and validated; the results of the validation tests are shown in Table 2 [17–19].

Analytical phase of the study

Within the scope of scientific work, one of the formulations of the drug "Glycine, sublingual tablets, 100 mg" of domestic production was tested for evaluation of release of its active substance in a medium simulating the human saliva as compared to analogues presented on the market. The profiles obtained are shown in Table 3.

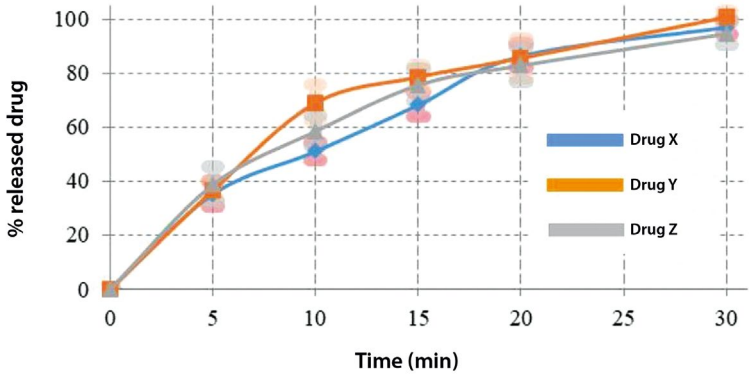
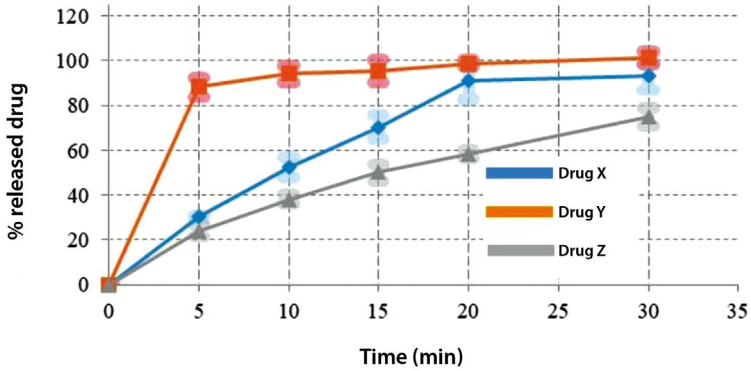
Table 2. **Major validation characteristics**

Validation characteristics	Description	Acceptability criterion	The results
Selectivity	5 calibration solutions were prepared of standard sample with known concentration; placebo solutions in dissolution medium, dissolution medium solutions with derivatizing agent added	The chromatograms of the solution for the specificity test should show no peaks with retention times of the substance glycine peak	Relevant
Calibration curve (linearity)	Calibration solutions were prepared in the concentration range of 10–110 % of the nominal concentration for the dosage 100 mg	Correlation coefficient $r \geq 0.98$; $-15\ \% \leq E, \% \leq 15\ \%$ – for concentrations at the lower limit of quantification, $-10\ \% \leq E, \% \leq 10\ \%$ – for concentrations of other points	Relevant, the analytical range was 10 to 110 % of the nominal concentration of tablets glycine in 100 mg
Accuracy/Trueness	Five series of test solutions were prepared, successively using the dissolution medium as a solvent. The obtained solutions were analyzed according to the conditions of analysis	$-15\ \% \leq E, \% \leq 15\ \%$ – for concentrations at the lower limit of quantification, $-10\ \% \leq E, \% \leq 10\ \%$ – for concentrations of other points	Relevant, average % openability lies within the confidence interval from 95.26 to 104.84 %
Precision	Five series of test solutions were prepared, successively using the dissolution medium as a solvent. The obtained solutions were analyzed according to the conditions of analysis	RSD ≤ 10 % – for concentrations at the lower limit of quantification, RSD ≤ 15 % – for concentrations of other points	Relevant, the relative standard deviation of glycine does not exceed the set value of 4 %

End of table 2

Validation characteristics	Description	Acceptability criterion	The results
Stability of samples at 37 °C for 24 hours	It was evaluated by the change in concentrations of the analyzed solutions, using for comparison samples of 100 % concentration level from the nominal for 100 mg dosage 24 hours after their preparation at room temperature and when heated at 37 °C in a desiccator (simulation of DKCT conditions)	–10 % ≤ E, % ≤ 10 % – for analyte concentrations	Relevant, test solutions are stable for 24 hours after preparation at room temperature and at 37 °C in a desiccator

Table 3. **Results of the DKCT**

Solution medium	Release profile
Purified water	
Simulated Saliva 5 pH 6.8	

The preparations tested in the experiment showed different dissolution rates, profile slopes and times of reaching the plateau. Preparations X and Y reached the release by 30th minute of testing. The release rate of preparation Y is higher than that of the other preparations. The profile curves of preparations X and Z rise considerably slower than the Y curve. For all the preparations tested similar relative standard deviation values at the ending time points were recorded.

Of particular note are the results obtained in the artificial saliva dissolution medium presented in Table 4.

The discriminatory nature of this dissolution medium allows evaluating the differences in technologies of producing a finished dosage form.

CONCLUSION

For the purposes of biopredictive testing of the drug "Glycine, sublingual tablets, 100 mg", a procedure of assay content was developed and validated. Analytical range of the method was between 10–110 % of the dosage form nominal concentration in 300 ml of the medium. The results of testing in the artificial saliva dissolution medium were more discriminative as compared to testing in purified water and allowed to find the differences in drug release efficiency, time of reaching the plateau, and slope of the dissolution profile curves.

The study of dissolution media that simulate the conditions of the oral cavity is an important aspect of biorelevant testing of sublingual and buccal dosage forms.

Table 4. Average amount of glycine released into Simulated Saliva 5 pH 6.8

Drug	Complete release, in %	Time to reach the plateau, min	RSD value by 30 min, in %
X	by 15 minutes – 71.55 by 30 minutes – 97.80	20	4.32
Y	by 15 minutes – 95.43 by 30 minutes – 101.33	5	2.84
Z	by 15 minutes – 50.01 by 30 minutes – 75.04	Doesn't reach the plateau	5.31

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