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Focused physicochemical stability study of reconstituted trastuzumab biosimilar SB3 (Ontruzant®) stored in the original vials over 28 days

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Abstract

Objective: Trastuzumab biosimilar SB3 (Ontruzant®), a HER2 binding monoclonal antibody, is available as powder for concentrate for solution for infusion. According to the summary of product characteristics, the reconstituted solution (21 mg/mL) is physicochemically stable for 7 days when stored refrigerated at 2–8 °C. The objective of this focused study was to determine the extended physicochemical stability of trastuzumab SB3 reconstituted with water for injection and stored in the original glass vials under refrigeration or at room temperature over a period of 28 days.

Methods: Ontruzant® vials were reconstituted with sterile water for injection and stored light protected at 2–8 °C in the refrigerator or at room temperature (15–25 °C, Ph. Eur.) over a maximum period of 28 days. At predefined time points (day 0, 7, 14, (21), 28) samples were withdrawn and analyzed by size-exclusion high-performance liquid chromatography with photodiode array detection, ultraviolet spectroscopy, and pH measurement. Test solutions were inspected for colour changes, clarity, and visible particles at each sampling time point.

Results: According to the size-exclusion chromatography assay, trastuzumab SB3 monomer concentrations exceeded 95 % of the initially measured concentrations over the entire study period. pH values and trastuzumab concentrations measured by UV remained unchanged. No colour changes or visible particles were detected. Results were independent from storage temperature.

Conclusions: According to the stability indicating methods used, physicochemical stability of reconstituted trastuzumab SB3 Ontruzant® solution in original glass vials is given over a period of 28 days either stored refrigerated or at room temperature. Results have to be substantiated by IE-HPLC or icIEF. To avoid microbiological instability storage under refrigeration is recommended.

Keywords: trastuzumab SB3; biosimilar; reconstituted solution; physicochemical stability; SE-HPLC

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Introduction

Trastuzumab, a humanized immunoglobulin G1 monoclonal antibody (mAb), binds to human epidermal growth factor receptor´s (HER2`s) extracellular domain thereby inhibiting growth of HER2 overexpressing tumour cells. In 2000, trastuzumab originator product Herceptin® (Roche Registration GmbH) was approved. Since 2017, several trastuzumab biosimilars were authorized by EMA. Trastuzumab reference and biosimilar products are approved for the treatment of adult patients with metastatic or early breast cancer or metastatic gastric cancer when tumours have HER2 overexpression or HER2 gene amplification [1].

In Europe, biosimilar medicinal products are licensed according to the EMA-Guidelines which are based on comparative quality, non-clinical, and clinical studies [2]. Due to the natural variability of the biological source and to the unique manufacturing process of each manufacturer, minor differences can occur between the biosimilar and its reference product. Minor variabilities, differences in the formulation and administration devices are allowed when scientific evidence shows that it does not affect safety, efficacy, and immunogenicity of the product [3]. Because of these variabilities, physicochemical in-use stability data cannot be extrapolated and must be experimentally tested for each finished reference and biosimilar brand product [4, 5]. In-use physicochemical stability data submitted by the manufacturer are assessed during the licensing process and published in the product-specific summaries of product

characteristics (SmPCs). In addition, stability studies are published in scientific journals, e.g. for the trastuzumab reference product Herceptin® [6–11] and the different trastuzumab biosimilar products [12–18]. In the SmPC of the trastuzumab biosimilar SB3 (Ontruzant®) is given that the reconstituted stock solution is physicochemically stable for 7 days when stored at 2–8 °C [1]. Yun et al. reported that the reconstituted SB3 solution is physicochemically stable for 3 days when stored at 25 ± 2 °C [12]. Data on extended physicochemical stability of reconstituted Ontruzant® solution are lacking and would facilitate efficient handling in pharmacy practice. Therefore, we designed a focused study on extended physicochemical stability of reconstituted SB3 solutions in the original vials over a period of 28 days either stored under light protection at 2–8 °C or at room temperature. For the focused study, size-exclusion high-performance liquid chromatography (SE-HPLC), ultraviolet (UV) spectroscopy, measurement of pH, and observation for visible particles and colour changes were chosen as analytical methods.

Materials and methods

Test solutions

Stability tests were performed with the authorized and marketed medicinal product Ontruzant® 150 and 420 mg powder for concentrate for solution for infusion. With six vials of Ontruzant® 420 mg (batch F1903258) SE-HPLC assay, pH measurement, visual inspection (series 1) and with six vials of Ontruzant® 150 mg (batch F2003096) UV spectroscopy (series 2) were performed. Each vial was reconstituted with 7.2 mL (for 150 mg) or with 20 mL (for 420 mg) water for injection (Aqua ad injectabilia, B Braun Melsungen AG, Germany, batch 184,228,091 and 2,24,518,091), resulting in concentrations of 21 mg/mL trastuzumab. Three vials of each series were either stored in the refrigerator (2–8 °C) or at room temperature (15–25 °C, Ph. Eur.) packed in lightproof plastic boxes.

Sampling time points

Samples for SE-HPLC and UV spectroscopy were withdrawn directly after reconstitution (d0) and at day 7, 14, 21, and 28 of storage. Measurement of pH was performed at the same time points except for day 21.

Sample preparation

For SE-HPLC 47.6 µL of trastuzumab test solution (21 mg/mL) was mixed with 952.4 µL of water for injection, resulting in samples of the nominal concentration 1.0 mg/mL. For UV spectroscopy 100 µL of trastuzumab test solution (21 mg/mL) was twice diluted 1:10 with 900 µL water for injection, resulting in samples of the nominal concentration 0.21 mg/mL.

SE-HPLC assay

Intact trastuzumab monomer soluble aggregates and fragments were determined by a stability indicating SE-HPLC assay with photodiode array detection, which was previously established by Kaiser et al. [6]. Acceptance criteria were set to a 5 % maximum loss of the monomer concentration and a 2 % maximum increase of secondary peak areas related to the main peak area [4]. Detailed characteristics of the SE-HPLC assay are given in Table 1. The SE-HPLC method used was validated according to the ICH Guideline Q2 (R1) [19]. Because a chemical reference standard was not available, validation was performed with Ontruzant® final medicinal product. Ontruzant® was reconstituted with water for injection and further diluted with water HPLC grade. Linearity of the method was evaluated with seven trastuzumab standard concentrations (0.5, 0.8, 0.9, 1.0, 1.1, 1.2, 1.5 mg/mL). Aliquots of each calibration standard were injected three times. The calibration curve was obtained by plotting the peak area against the nominal trastuzumab concentration. Intraday and interday accuracy and precision of the SE-HPLC assay were validated by analysing 10 trastuzumab solutions (1.0 mg/mL) on five consecutive days. Test solutions were freshly prepared every day. Test solution numbers 1 and 10 were injected tenfold, and test solution numbers 2–9 were injected single fold on days 1–5.

UV spectroscopy

Trastuzumab concentrations were measured by an Evolution 201 UV–vis Spectrophotometer (Thermo Fisher Scientific, serial number 5A3P172004, Schwerte, Germany). Prepared samples were transferred to a High Precision Cell made of Quartz SUPRASIL® (Light Path, 10 mm, Hellma Analytics, article no. 104-10-40) and absorption was determined at 280 nm wavelength. Water for injection (Aqua ad injectabilia, B Braun Melsungen AG, batch 2,24,518,091) was used as blank reference. The UV method used was validated according to the ICH Guideline Q2 (R1) [19]. For linearity testing, trastuzumab concentrated solution was diluted with water HPLC grade, resulting in seven calibration standards (0.105, 0.168, 0.189, 0.210, 0.231, 0.252, 0.315 mg/mL). Each standard solution was measured three times. The calibration curve was obtained by plotting extinction against the nominal concentration. Accuracy and interday precision were analyzed in parallel. Therefore, three standard solutions

Table 1: Characteristics of the SE-HPLC assay.

	SE-HPLC (based on Kaiser et al. [6])
Column	TSKgel G3000SWXL 7.8 × 300 mm, 5 µm, Tosoh bioscience
Column temperature	25 °C
Sample temperature	5 ± 2 °C
Mobile phase	0.2 M KH_2PO_4 solution + 0.2 M NaOH solution (pH 7.2)
Gradient profile	Isocratic
Flow rate	1.0 mL/min
Injection volume	20 µL
Injections per vial	3
Run time	20 min
Retention time	About 8.5 min
Detection wavelength	214 nm

SE-HPLC, size-exclusion high-performance liquid chromatography.

(0.168, 0.210, 0.252 mg/mL) were freshly prepared in triplicate. Each standard solution was measured three times, resulting in nine measurements per concentration. For interday precision three samples with the concentration of 0.210 mg/mL were freshly prepared and measured in triplicate on each of five consecutive days. Acceptance criteria was defined as less than 10 % loss of trastuzumab concentrations.

pH measurement

pH measurements were performed with the pH 210 Microprocessor pH meter (Hanna Instruments, Kehl am Rhein, Germany) equipped with an InLab Micro pH glass electrode (Mettler Toledo, Greifensee, Germany). The pH meter was calibrated with standard buffer solutions pH 4.01 (DuraCal buffer, Hamilton Bonaduz AG; batch 1,720,122) and pH 7.00 (DuraCal buffer, Hamilton Bonaduz AG; batch 111,005,562) whenever test solutions were measured. Each sample of undiluted test solutions was measured three times. Acceptance criteria for stability was defined as not more than 0.5 pH unit change over the 28 day study period [4].

Appearance

According to the SmPC, trastuzumab lyophilized powder is supposed to be white to pale yellow. After reconstitution, it results in a colourless to pale yellow transparent solution [1]. Whenever samples from test solutions were withdrawn, test solutions were visually examined with the unaided eye for visible particles and colour changes. Test solutions without any changes were defined as physicochemical stable.

Results

SE-HPLC

In the SE-HPLC chromatograms of trastuzumab Ontruzant® test solutions a sharp main peak related to the trastuzumab monomer was detected at the retention time (R_t) of approximately 8.5 min, a small peak with R_t of about 12 min related to the excipient histidine, and a very small peak at the R_t of about 5 min, most likely related to an higher molecular weight product (HMWP) (see Figure 1). The correlation coefficient of the trastuzumab assay amounted to R^2=0.9874 and proved linearity over the tested concentration range. The mean trastuzumab concentration of the intraday precision test was 1.014 mg/mL (101.4 %) ± 0.57 % relative standard deviation (RSD). The interday precision tests revealed a mean trastuzumab concentration of 1.002 mg/mL (100.2 %) ± 1.46 % RSD. Results deviated less than 2 % and proved reproducibility.

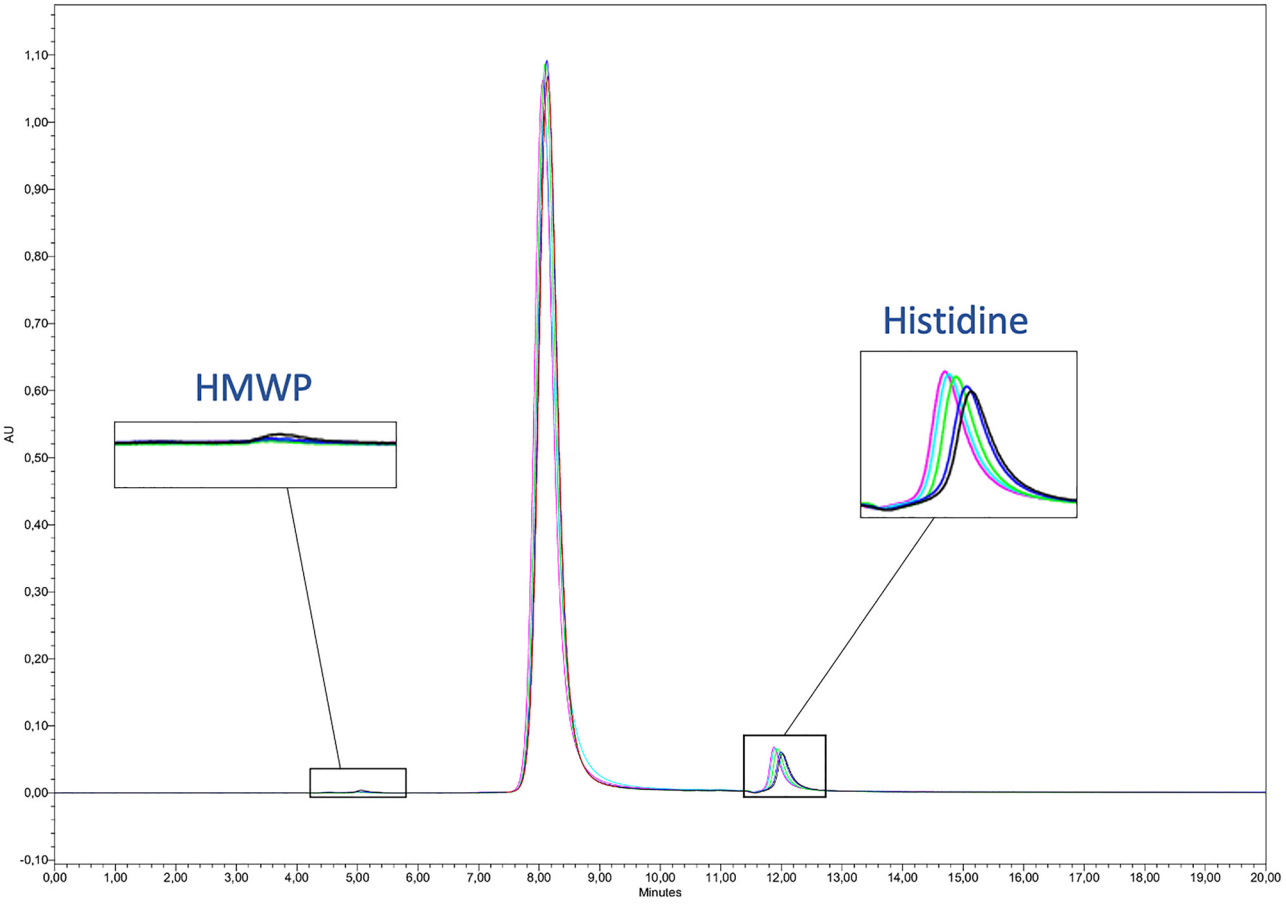

Figure 1: Overlay of SE-HPLC chromatograms of trastuzumab SB3 solution (1.0 mg/mL) d0, d1, d7, d14, d21, d28. Main peak with high molecular weight product (HMWP) and histidine at detection wavelength 214 nm.

All monomer peaks of the test solutions stored at 2–8 °C or at 15–25 °C were inspected for changes in peak area, peak height and for the formation of additional secondary peaks in form of HMWPs and low molecular weight products (LMWPs). No substantial or systematic changes could be detected in the test solutions over the entire 28-day storage period. All main peaks and secondary peaks met the acceptance criteria (main peak deviation ≤5 %, secondary peaks maximum of 2 % in relation to the main peak). Detailed results are shown in Table 2.

UV spectroscopy

The correlation coefficient of the assay amounted to R^2=0.9998 and proved linearity over the tested concentration range. Accuracy of the assay was determined by the calculation of the percentage rate of recovery for each concentration tested and amounted to 99.7 ± 0.3 % resulting from nine measurements per concentration. Intraday reproducibility showed relative standard deviations of 0.4 % for 0.168 mg/mL, 0.2 % for 0.210 mg/mL, and 0.3 % for 0.252 mg/mL test solutions. Interday precision, expressed as relative standard deviation of the mean values of five consecutive days, was 1.1 % and therefore proved reproducibility.

Detailed results of the UV assay are given as percentage rate of the initial trastuzumab concentration (Table 3). Trastuzumab concentrations remained unchanged (99.68–101.80 %) and within the specification (≥90 % of the initial concentration) at both storage conditions over the 28 day study period.

pH measurement and appearance

Results of the pH measurements are shown in Table 4. Trastuzumab pH values remained stable (6.22–6.27) and remained within the specification (<0.5 pH unit changes) during the study period of 28 days. Because inter-individual deviations of the measurements were low (SD≤0.02), standard deviations were not listed in Table 4. The appearance of trastuzumab test solutions remained unchanged and revealed no visible particles or colour changes within the observation period.

Discussion

In-use stability data of mAb containing reference or biosimilar medicinal products need individual testing because of their complexity and heterogeneity [4, 20]. For the same reasons, physicochemical stability of (glyco)proteins such as mAbs is determined by orthogonal analytical methods.

Table 2: Stability of trastuzumab SB3 reconstituted in the original vial stored at 2–8 °C and 15–25 °C over 28 days determined via SE-HPLC. Results expressed as % remaining trastuzumab concentration ± SD (n=9), initial concentration day 0 set as 100 %.

Storage temperature	SE-HPLC assay						
	Initial trastuzumab monomer concentration, mg/mL ± SD (n=9)		Trastuzumab concentration remaining ± SD (n=9); measured concentration day 0=100 %				
	Nominal	Measured (day 0)	d1	d7	d14	d21	d28
2–8 °C	21	20.66 (±0.29)	98.87 (±1.88)	99.22[a] (±1.84)	101.77 (±2.17)	102.24 (±0.99)	100.83 (±1.78)
15–25 °C	21	20.59 (±0.11)	100.29 (±0.73)	100.84 (±1.38)	101.47 (±0.70)	101.76 (±0.69)	102.22 (±0.58)

[a]n=8. SE-HPLC, size-exclusion high-performance liquid chromatography; SD, standard deviation.

Table 3: Stability of trastuzumab SB3 reconstituted in the original vial stored at 2–8 °C and 15–25 °C over 28 days. UV spectroscopy results expressed as % remaining trastuzumab concentration ± SD (n=9), initial concentration day 0 set as 100 %.

Storage temperature	UV spectroscopy						
	Initial trastuzumab concentration, mg/mL ± SD (n=9)		Trastuzumab concentration remaining ± SD (n=9); measured concentration day 0=100 %				
	Nominal	Measured (day 0)	d1	d7	d14	d21	d28
2–8 °C	21	20.94 (±0.05)	100.58 (±0.67)	101.54 (±0.47)	100.27 (±0.25)	99.68 (±0.55)	99.95 (±0.42)
15–25 °C	21	21.08 (±0.10)	101.80 (±0.86)	100.37 (±1.21)	100.37 (±0.32)	100.42 (±0.35)	99.95 (±0.35)

SD, standard deviation.

Table 4: pH of trastuzumab SB3 stock solution reconstituted in the original vial stored at 2–8 °C and 15–25 °C over 28 days. Results expressed as mean pH.

Storage temperature	pH				
	d0	d1	d7	d14	d28
2–8 °C	6.27	6.22	6.24	6.27	6.24
15–25 °C	6.27	6.25	6.25	6.26	6.25

Out of the recommended orthogonal analytical methods we focused on SE-HPLC, UV-spectroscopy, and pH measurement to determine the integrity of trastuzumab SB3. These stability-indicating methods were chosen for the extended in-use stability study as physicochemical stability of reconstituted and diluted trastuzumab SB3 was already comprehensively investigated using these methods among others [12]. SE-HPLC is well accepted to investigate the intact tertiary structure of mAbs and the absence of oligomers and soluble aggregates. We used previously the same SE-HPLC method for the stability testing of trastuzumab reference product and proved the stability indicating nature by forced degradation studies [6]. Concurrent validation of the SE-HPLC and UV assay were based on the ICH Q2 (R1) guideline [19]. Acceptance criteria for the assessment of stability, sample numbers, sampling time points and storage conditions were chosen based on the specifications of the NHS Pharmaceutical Quality Assurance Committee [4].

Many studies showed physicochemical stability of trastuzumab reference product and various biosimilars. According to the methods used in our study, reconstituted trastuzumab SB3 (Ontruzant®) solution stored in the original glass vials revealed to be physicochemically stable over a period of 28 days regardless of the storage temperature. Impurities and degradation products were not detected. Yun et al. reported physicochemical stability data of reconstituted trastuzumab SB3 solution (3 days at 25 °C) and diluted trastuzumab SB3 infusion solution (28 days at 5 °C and 25 °C) [12]. The SE-HPLC assays of reconstituted SB3 solutions were identical in both studies during the first 3 days and did not change in our study over the extended test period of 28 days. No significant changes of the trastuzumab peak and no additional secondary peaks got obvious indicating the absence of fragmentation or aggregation. The LMWP peak at R_t 12 min was assigned to histidine which is used as a common excipient in the formulation of final medicinal mAb products [21]. pH values (6.22–6.27) remained unchanged over the extended test period and corresponded to those measured by Yun et al. in the reconstituted trastuzumab SB3 solution (pH 6.1–6.2) [12]. In addition, no change in colour, clarity, or particulate matter could be observed in both studies. Furthermore, there is evidence that higher concentrations of mAb solutions show less degradation tendencies than lower concentrations, which could be related by container absorption or the dilution of stabilising excipients [4]. The extended physicochemical stability of reconstituted, concentrated trastuzumab SB3 solution is in agreement with the previously proven stability of diluted trastuzumab SB3 infusion solution [12]. Results were independent from the chosen storage temperature (2–8 °C, room temperature) in both studies.

Limitations

Physicochemical stability of proteinaceous medicinal products should be studied by orthogonal methods. Out of the highly recommended and utilized methods [4, 7, 8, 12, 14–18, 20, 22] ion-exchange high-performance liquid chromatography (IE-HPLC) or imaged capillary isoelectric focusing (icIEF) were not used in this study to investigate possible changes in charge variants (acidic, main, and basic variants). Although, Yun et al. showed by icIEF that the initial isoform pattern did not change in diluted trastuzumab SB3 solutions for 28 days [12] and because the utilized UV spectroscopy method only indicates the protein content, additional IE-HPLC or icIEF are necessary to substantiate stability of reconstituted trastuzumab SB3 over 28 days. Subvisible particle measurement and submicronic aggregation were not tested in our study due to the limited available volume of trastuzumab SB3 reconstituted solution.

Finally, microbiological and physicochemical stability are to be considered concurrently when determining the stability of an individual mAb preparation. Microbiological stability of trastuzumab was tested by Karstens et al. by intended inoculation of trastuzumab diluted solution with various facultative pathogenic microorganisms [23]. Tested strains remained viable but did not show any pronounced growth supporting activity in trastuzumab solutions over the observation period. Therefore, refrigerated storage is recommended inhibiting growth of contaminating mesophilic microbes. Nevertheless, the reconstituted trastuzumab solution can still be used after a temporary interruption of refrigerated storage thus preventing waste and promoting efficiency.

Conclusions

According to the stability indicating methods used, physicochemical stability of reconstituted trastuzumab SB3

Ontruzant® solution in original glass vials is given over a period of 28 days either stored refrigerated or at room temperature. No significant changes could be observed by the analytical methods used. However, additional experimental testing of changes in charge variants over the 28 day period should be added to substantiate the findings. From a microbiological point of view, refrigerated storage is recommended. Results promote a more efficient handling in terms of costs, environment, and practicability in everyday pharmacy practice without compromising safety and efficacy of trastuzumab SB3 preparation.

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Data availability: The raw data can be obtained on request from the corresponding author.

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