Original Article

Advancing USP compendial methods for fixed dose combinations: A case study of metoprolol tartrate and hydrochlorothiazide tablets

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ABSTRACT

The current United States Pharmacopeia–National Formulary (USP–NF) includes more than 250 monographs of fixed dose combinations (FDCs), and some of them need to be updated due to incompleteness of impurity profiles and obsolescence of analytical methodologies. A case study of metoprolol tartrate and hydrochlorothiazide tablets is presented to summarize challenges encountered during the USP monograph modernization initiative of FDCs and to highlight an “adoption and adaptation” approach employed for method development. To this end, a single stability-indicating HPLC method was developed to separate the two drug substances and eight related compounds with resolution 2.0 or higher between all critical pairs. Chromatographic separations were achieved on a Symmetry column (C18, 100 mm × 4.6 mm, 3.5μm) using sodium phosphate buffer (pH 3.0; 34 mM) and acetonitrile as mobile phase in a gradient elution mode. The stability-indicating capability of this method has been demonstrated by analyzing stressed samples of the two drug substances. The developed HPLC method was validated for simultaneous determination of metoprolol tartrate and hydrochlorothiazide and relevant impurities in the tablets. Moreover, the developed method was successfully applied to the analysis of commercial tablet dosage forms and proved to be suitable for routine quality control use. The case study could be used to streamline USP’s monograph modernization process of FDCs and strengthen compendial procedures. © 2019 Xi’an Jiaotong University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

A fixed dose combination (FDC) is a formulation that combines two or more active pharmaceutical ingredients (APIs) in a single dosage form, which is manufactured and distributed in fixed doses. FDCs have been increasingly used in the treatment of a wide range of conditions because of the tremendous benefits the combination brings, such as the reduced “pill burden” of patients, the improved efficacy, a reduced incidence of adverse effects, and the lower costs of manufacturing [1]. In addition, the development and marketing of FDCs have been an effective strategy to extend the drug patent and exclusivity life of pharmaceuticals [2]. Compared with single-ingredient drug products, FDCs raise more quality issues as APIs in the FDCs have to be physically and chemically compatible along with their excipients. It is important to ensure that these APIs do not generate new impurities or raise unexpected drug-drug chemical interactions [3–6]. Controlling the quality of FDCs is becoming increasingly important from a public health perspective. For example, India has recently been flooded with FDCs that contain banned, restricted or never-approved drugs due to the discrepancy in law enforcement between the state and central regulators; the Indian Health Ministry responded to the crisis by banning 334 FDCs in early 2016 to safeguard public interest [7].

FDCs in the US market are legally required to conform to the relevant standards in the United States Pharmacopeia–National Formulary (USP–NF) to ensure identity, strength, quality, and purity of finished products for public health [8]; and as such it is critical to keep USP FDC monographs scientifically up to date. Currently in the USP–NF there are more than 250 monographs of FDCs [9], which account for approximately 5% of total monographs. Some of these monographs include separated assay procedures for each API and incomplete or inconsistent impurity tests. The outdated monographs have raised concerns from the U.S. Food and Drug Administration (FDA) and USP stakeholders that those procedures do not reflect current practices of industry [10]. In response to these concerns, USP launched an initiative of monograph modernization in 2009 to strengthen the public standards by improving the outdated compendial procedures [11,12]. Specifically, USP is systematically replacing outdated technology and methodologies with more current procedures and adding critical
tests (e.g., impurities) to the monographs [13,14]. Modernizing FDC monographs has been an integral part of the initiative; in fact, products with multiple and atypical active ingredients and interfering excipients are on the prioritized list of monographs requiring modernization as posted on the USP’s website [15].

In addition to collaborating with the FDA and pharmaceutical industry and soliciting donations of analytical procedures to support modernization, USP has also been actively engaged in the initiative using its own laboratories since 2010. The work described here represents efforts undertaken at the USP Compendial Development Laboratory (CDL) to modernize an FDC monograph. Strategic approaches were highlighted to align with the general technical goals including: (1) a single HPLC procedure for both organic impurities and assay in a monograph, (2) the same method for a family of products of the same API, and (3) preferred adoption or modification of existing compendial methods [13].

The USP metoprolol tartrate (MT) and hydrochlorothiazide (HCTZ) tablets monograph describes two HPLC–UV methods for the assay of MT and HCTZ [16]. The assay procedure for MT is the same as that of the MT injection monograph and the sample preparation involves a liquid–liquid extraction prior to chromatographic analysis [17]. The assay procedure for HCTZ is different from any compendial methods of HCTZ drug substance [18] or drug products (tablets and capsules) [19,20]. Moreover, this monograph lacks a procedure for organic impurities. This drug product is not included as a monograph in the other major pharmacopeias. The USP MT monograph lists USP Related Compounds (RC) A, B, C, and D as specified impurities [21], while the HCTZ monograph includes specified impurities of chlorothiazide (CTZ), 5-chlorohydrochlorothiazide (5-CHT), benzothiadiazine RC A (BT RC A), and hydrochlorothiazide dimer (HCTZd) [18]. There have been numerous publications reporting on chromatographic determination of HCTZ and other drug substances in FDCs [22]; however, developing a single method as both organic impurity and assay procedure was rarely delineated [23,24]. An extensive review of the literature revealed that no method has been reported for the quantitation of MT and HCTZ and their known impurities in MT and HCTZ tablets. The primary objective of this study was to develop a single stability-indicating HPLC method for both assay and organic impurities testing of the FDC. The chemical structures of MT and HCTZ and their process and degradation related substances are shown in Fig. 1.

2. Experimental

2.1. Chemicals and reagents

Drug substances MT, HCTZ, RC A, B, C, and D, CTZ, and BT RC A were obtained from USP Reference Standards (Rockville, MD, USA). Drug products MT and HCTZ tablets (Manufacturer 1, 100 mg MT and 25 mg HCTZ, Lot: 3051465; Manufacturer 2, 50 mg MT and 25 mg HCTZ, Lot: 1405001848; Manufacturer 3, 50 mg MT and 25 mg HCTZ, Lot: GKN0043) were obtained from suppliers. 5-CHT and CHTZd were purchased from Toronto Research Chemicals (Toronto, Canada). Hydrogen peroxide (∼30%) was purchased from Sigma-Aldrich (St. Louis, MI, USA). Acetonitrile (LC/MS grade), hydrochloric acid (37.5%), Sodium hydroxide solution (10 N NaOH, J.T. Baker), sodium phosphate monobasic (anhydrous, ≥99%), and phosphoric acid (85%) were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Deionized water was purified with a Milli-Q plus system from Millipore (Billerica, MA, USA).

2.2. Instrument and analytical parameters

HPLC analysis was performed on an Agilent 1200 Infinity HPLC (Santa Clair, CA USA), or a Waters Acquity UPLC, H-Class (Milford, MA, USA). Data acquisition, analysis, and reporting were
performed using Waters Empower 3. Separations were carried out on a Waters Symmetry C18 column (4.6 mm × 100 mm, 3.5 μm) using a mobile phase system consisting of sodium phosphate buffer (pH 3.0: 34 mM; A)–acetonitrile (B) at a gradient elution: 0–4 min, 15% B; 4–10 min, 15%–90% B; 10.0–10.1 min, 90%–15% B; 10.1–13 min, 15% B. GL Sciences Inertsil ODS-3 column (4.6 mm × 100 mm, 3 μm) was used as an alternative column. Analyses were performed at ambient temperature with a flow rate of 1.0 mL/min. Sampler was cooled to 4 °C. Analytical parameters were subjected to variations during method development and robustness studies. Spiked solutions used for method validation were prepared using a Hamilton Microlab 600 Diluter (Reno, NV, USA). Photostability was performed on a Caron Photostability Chamber (Marietta, OH, USA). Thermal and humidity stress was performed on an ESPEC Humidity Chamber (Hudsonville, MI, USA).

2.3. Preparation of mobile phase and diluent

Mobile phase A was sodium phosphate buffer (pH 3.0; 34 mM), which was prepared by dissolving sodium phosphate monobasic in water; buffer pH was adjusted to 3.0 using phosphoric acid. Mobile Phase B was acetonitrile. A solution of mobile phase A and acetonitrile (85:15, v/v) was used as the diluent.

2.4. Forced degradation experiments

The forced degradation studies were performed separately for MT, HCTZ, and a mixture of MT and HCTZ (1:1, w/w) under oxidative, thermal, thermal and humidity, hydrolytic, and light stress conditions. Oxidative and hydrolytic stresses were performed by treatment of material(s) (1 mg/mL) with 0.1 M HCl, 0.1 M NaOH, and 3% hydrogen peroxide at ambient temperature for 3 days. Light stress was performed by exposure of material(s) to 200 W-h/ square meter ultraviolet light (UV) and then to 1.2 million lux-h white light (Vis). Thermal stress was conducted by storing of material(s) in a 105 °C humidity chamber for 3 days. Thermal and humidity stress was conducted by exposure of the material(s) to 80 °C temperature and 85% relative humidity for 3 days. On the day of analysis, each of the stress samples was diluted or dissolved to make a sample solution having a concentration of 0.05 mg/mL.

2.5. Standard solutions

The system suitability solution (0.1 mg/mL for APIs and 0.01 mg/mL for impurities) was prepared by dissolving MT, HCTZ and RC C, BT RC A, CTZ, and 5-CHT in the diluent. An impurity stock solution (50 μg/mL for MT and RC C and 25 μg/mL for HCTZ and BT RC A) was prepared by dissolving the four materials in the diluent. The standard solution (1.0 μg/mL for metoprolol and RC C and 0.5 μg/mL for HCTZ and BT RC A) was prepared by sequential dilution of the impurity stock solution. Linearity solutions were prepared at 0.1%, 0.25%, 0.5%, 0.75%, and 1.5% impurity level of the sample concentration by diluting the impurity stock solution. The standard solution for assay procedure (0.1 mg/mL for metoprolol and 0.05 mg/mL for HCTZ) was prepared by dissolving MT and HCTZ in the diluent. Assay linearity solutions at 70%, 85%, 100% 115%, and 130% levels were prepared by sequentially diluting a stock linearity solution (130%, 0.13 mg/mL for MT and 0.065 mg/mL for HCTZ), which was prepared by dissolving MT and HCTZ in the diluent.

2.6. Sample solutions

The composite of MT and HCTZ tablets was prepared by grinding and homogenizing 20 tablets to a fine powder. A sample solution for organic impurities procedure (1.0 mg/mL for MT and 0.5 mg/mL for HCTZ) was prepared by dissolving a portion of the composite in the diluent. Sample solutions for products with different strengths were prepared in the same fashion as described above. A sample solution for assay (0.1 mg/mL for MT and 0.05 mg/mL for HCTZ) was prepared at the same concentration as standard solution for assay using the composite. Assay sample solutions for products with different strengths were prepared in the same fashion as described for a sample solution for assay.

3. Results and discussion

3.1. Method development

It is challenging to develop a single and quality control friendly HPLC method for an FDC to separate all impurities as the number of analytes to be dealt with increases and chemical properties of these APIs and impurities may vary markedly. Previous studies on FDCs indicated that chromatographic variables, especially mobile phase composition and buffer pH, could have profound effects on the ionization of analytes and the resultant chromatographic properties [23,24]. Another critical parameter for chromatographic analysis of FDCs is the UV wavelength for detection. Although both MT and HCTZ and their impurities have UV absorbance around 223 and 270 nm, the optimal wavelength for detection was determined to be 223 nm as all compounds have similar absorbance at this wavelength (Fig. S1). In contrast, all components showed varied intensity at 270 nm that would result in greater variability in response factors.

The method development initially focused on the separation of the two APIs and all known impurities; accordingly, a method development solution was prepared including the two APIs and RCs A, B, C, and D, and CTZ, 5-CHT, HCTZd, and BT RC A. The initial studies indicated that the method development solution should be freshly prepared and analyzed as HCTZd degrades rapidly to HCTZ at room temperature [25].

Adoption or modification of existing compendial methods is one of the preferred strategies for USP monograph modernization. When full adoption of a pharmacopeial procedure is not feasible, an alternative approach could be employed by adapting some elements (column, mobile phase, elution mode) of the procedure. This “adaptation and adaptation” approach is very efficient for method development because existing compendial methods have been validated, tested, and proved to be reliable and robust; additionally, modification of those methods for the same APIs has a high probability of success. The preliminary investigation indicated that neither of two USP assay methods of the FDC was able to separate all impurities [16]; hence, other existing USP compendial methods of relevant monographs of metoprolol or HCTZ drug substance and drug products were screened.

The USP MT monograph describes an HPLC procedure that separates metoprolol and its specified impurities (RC A–D) [21]. The method was also adopted or modified for metoprolol drug substances [26] and drug products [27,28]. Separation of metoprolol and its impurities was achieved on a Zorbax C8 (150 mm × 4.6 μm, 5 μm) column and a mobile phase consisting 60% sodium dodecyl sulfate buffer and 40% acetonitrile. The direct application of the method to the method development solution resulted in co-elution of HCTZ with CTZ and BT RC A, indicating the unsuitability of the method for the separation of HCTZ impurities. Complete separations were achieved by converting of the isocratic elution to a gradient mode; however, resolution of metoprolol impurities was compromised and peak broadening of HCTZ and its impurity peaks was observed. Next, a “focused column screening” was conducted using similar Zorbax columns from the same manufacturer. The underlying rationale is that the basic silica
The forced degradation studies were performed in parallel for MT, HCTZ, and a mixture of MT and HCTZ under oxidative, thermal, thermal and humidity, hydrolytic, and light stress conditions (Section 2.4). Significant degradation was observed for the mixture sample under the thermal and humidity (20.6%), base (4.9%), and oxidative (5.1%) stress conditions (Tables S1 and S2). No degradation was detected under thermal, acid, and light stress conditions. All the new peaks (%TDA ≥ 1%) were separated from the main peaks and all other impurities at resolution of 2.0 or higher. In addition, the main peaks were found to be spectrally pure based on PDA purity and spectral library match analysis.

The degradation results for the combined APIs were generally consistent with these of individual API, and only one exception was observed: the degradation of HCTZ to BT RC A was significantly boosted under heat and humidity stress conditions; about 1% of BT RC A was generated from sole HCTZ, whereas the combined APIs yielded 20.6% of the same degradant under the identical conditions (Table 1). The remarkable stability difference between HCTZ and the mixture of MT and HCTZ suggested that MT must have played a critical role in the degradation process. Furthermore, water proved to be essential for the process as no significant degradation was detected for both samples under thermal stress (Table 1). We reasoned that the tartaric acid may function as a Bronsted acid [29,30] to activate the sulfone group of HCTZ and catalyze the hydrolysis of HCTZ in the presence of water [31,32] (Fig. 3). This finding implies that such drug-drug chemical interactions could occur under certain storage conditions for MT and HCTZ tablets. Interestingly, physical and chemical stability and compatibility issues were commonly observed for FDCs under thermal and humidity conditions [33,34]. The stress studies especially the observed chemical interactions clearly established the sense of urgency and importance of developing a stability- and purity-indicating method as a compendial procedure for this FDC.

3.3. Method validation

The method was developed to ensure that it satisfies the specificity requirements for all impurities (Table S3). Validation of the method as an organic impurity procedure was only performed for degradation products. USP and British Pharmacopeia monographs of MT or HCTZ drug products listed RC C and BT RC A as the specified impurities for MT and HCTZ [17,18,35–37], respectively. Our forced degradation studies also revealed BT RC A as major degradants, and no other known impurities were detected as

![Fig. 2. Typical chromatogram of the method development solution (separation of MT, HCTZ, and eight impurities). Chromatographic conditions: Waters Symmetry C8 column, 100 mm × 4.6 mm, 3.5 μm. Mobile phase A: sodium phosphate buffer, pH 3.0; 34 mM. Mobile phase B: acetonitrile. Gradient: 0.0–4.0 min (15% B), 4.0–10.0 min (15%–90% B), 10.0–10.1 min (90%–15% B), and 10.1–13 min (15% B). Column temperature: ambient. Sample temperature: 4 °C. Flow rate: 1.0 mL/min. Injection volume: 10 μL. Detection: 223 nm. M = metoprolol.](image-url)
degradants. As process impurities are controlled in drug substances [38], metoprolol RC C, and BT RC A were selected as specified impurities for the proposed method.

3.3.1. Specificity

The specificity of the method was demonstrated by analyzing diluent, standard solution, sample solutions, and spiked sample solutions containing known impurities. No peak at retention time of any known impurity and APIs was observed in the diluent injection. No interference to API peaks and known impurity peaks was detected for sample solutions. The resolution values between each of the adjacent impurity peaks, and between API and adjacent peaks were greater than 2.0 (Tables S4 and S5). The homogeneity of the peak purity of the MT and HCTZ peaks in three representative tablets was estimated on the basis of a photodiode-array (PDA) scan from 210 to 400 nm.

3.3.2. Linearity

Two separate linearity curve sets were created for impurities and assay procedures. The impurities method was validated in the range of impurity level 0.1%–1.5% of nominal concentration of the sample solution at 1.0 mg/mL for MT and 0.5 mg/mL for HCTZ. The correlation coefficient for regression analysis of theoretical concentration versus the experimental concentration was greater than 0.999 (Table S6). The linearity was demonstrated as the values of norm intercept–slope for all components were within ± 1%. The relative response factors of the two impurities were determined on the basis of the slope of linearity as 1.08 for metoprolol RC C, and 1.24 for BT RC A. The linearity for assay was evaluated covering 70%–130% of the normal concentration of sample solution at 0.1 mg/mL for metoprolol and 0.05 mg/mL for HCTZ. The corresponding correlation coefficient was also greater than 0.999 for both MT and HCTZ, and the values of norm intercept–slope for the two APIs were within ± 2% (Table S7).

3.3.3. Accuracy, precision, and intermediate precision

The accuracy of the impurities method was established by evaluating recoveries obtained with spiked solutions at 0.1%, 0.75%, and 1.5% impurity levels. Precision was estimated by evaluating six spiked solutions at 0.1% impurity level. Recovery was calculated by comparing the theoretical concentration calculated from the calibration curve and the nominal concentration. The results of accuracy and precision analyses are summarized in Table S8. The accuracy of the method was established by the fact that recoveries across all data points were between 91.7% and 104.1%. The precision of the method was confirmed in that RSD (%) values of the two impurities at 0.1% level were less than 6%. These data indicated that the method is reliable and repeatable for simultaneous quantitation of the RC C and BT RC A. Intermediate precision was determined by another scientist on a different instrument on a different day using an alternative column (GL Sciences Inertsil ODS-3). The accuracy and precision results from intermediate precision also met the criteria. The average combined recoveries of 12 injections at 0.1% level including intermediate precision were 101.7% for RC C and 99.2% for BT RC A, and the combined RSDs (%) for the two impurities were less than 5%.

The accuracy of the assay procedure was assessed using six sample solutions as repeatability solutions, and triplicate spiked solution at 110%, 120%, and 130% levels. The average assay results of repeatability were 99.7% for MT and 97.9% for HCTZ, and RSDs (%) were less than 2% for both APIs (Table S9). The recovery was determined by comparing the amount measured with the average of drug product assay value, derived from the repeatability result, and the spiked amount. The accuracy was verified as recoveries of MT and HCTZ at each level were within 100 ± 2% (Tables S10–S12).

3.3.4. Solution stability

The solution stability was determined by monitoring the standard solution and 0.1% spiked solution at 4-h intervals over a period of 24 h. No degradation trend was observed for any of the compounds of interest. As sampler temperature was kept at 4 °C, the sample of standard solution and spiked solution at 0.1% level were stable for 24 h (Peak area changes of metoprolol, HCTZ, RC C, and BT RC A from the initial time point were less than 10% (Table S13)). The standard solution and sample solution for assay were also stable for 24 h (Table S14).

3.3.5. Robustness

A robustness solution that contains MT, HCTZ, RC C, BT RC A, CTZ and 5-CHT was used for robustness study under the variations of column temperature, flow rate, mobile phase B content, and an alternate column. Results were evaluated for system suitability parameters including retention time, relative retention time, resolution, and peak tailing (Table S15). Results showed that minor variation of chromatographic parameters did not lead to any system suitability failure and all acceptance criteria were met.

Table 1

| Substances | Stress conditions | Generation of BT RC A |
|------------|------------------|-----------------------|
| HCTZ       | 105 °C, 3 days   | < 1%                  |
|            | 85 °C, 80% RH, 3 days | ~ 1%                 |
| MT and HCTZ| 105 °C, 3 days   | < 1%                  |
|            | 85 °C, 80% RH, 3 days | 20.6%                |

Fig. 3. A proposed pathway for the degradation of HCTZ to BT RC A under thermal and humidity conditions.
3.4. Application

To demonstrate the suitability and applicability of the method, three commercial MT and HCTZ tablets samples from different manufacturers were tested. The organic impurities test indicated that only BT RC A (0.02%) was detected in a product and was within the proposed limit (1.0%) (Table S16). The assay results of the three manufacturers showed that both MT and HCTZ were within 98.3%-102.4% (Tables S10 and S17) and met the pharmacopeial requirements (90.0%-110.0%).

3.5. Status of the procedure

The proposed procedure was published for public review and comments in Pharmacopoeial Forum (PF) 42(4) in September–October 2016 [39], and became official as December 1, 2017 [40].

4. Conclusions

A single HPLC method was developed for MT and HCTZ tablets. The developed method is capable of separating the two APIs (MT and HCTZ) and eight related compounds within a short time frame, and could be used as a procedure for both organic impurities and assay testing. The case study highlights the general goals and strategies of USP monograph modernization of FDCs. Given the complicated nature of method development for FDCs, the proposed "adoption and adaption" approach could be used to streamline the USP monograph modernization of FDCs, and provides a powerful solution to expediting the overall modernization process.

Conflicts of interest

The author declares that there are no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jpha.2018.12.003.

References

[1] T.T. Karafili, K. Sedo, J. Bossart, Fixed-dose combination products – a review, Drug Dev. Deliv. 14 (2014) 32–55.
[2] J. Hao, R. Rodriguez-Monguio, F. Seoane-Vazquez, Fixed-dose combination drug approvals, patents and market exclusivities compared to single active ingredient pharmaceuticals, PLoS One 10 (2015) 1–13.
[3] Food and Drug Administration (FDA), Guidance for industry: Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV, Center for Drug Evaluation and Research, Rockville, Maryland, 2006.
[4] Food and Drug Administration (FDA), Guidance for Industry: New Chemical Entity Exclusivity Determinations for Certain Fixed Combination Drug Products, Center for Drug Evaluation and Research, Rockville, MD, 2014.
[5] WHO expert committee on specifications for pharmaceutical preparations, WHO Technical Report Series 925: Guidelines for Registration of Fixed-Dose Combination Medicinal Products, Geneva, Switzerland, 2005.
[6] European Medicines Agency (EMA), Guideline on clinical development of fixed combination medicinal products, London, England, 2009.
[7] [http://www.rsc.org/chemistryworld/2016/03/india-bans-combination-drugs].
[8] Food and Drug Administration (FDA), Federal Food Drug and Cosmetic Act, 21 USC Chapter V, 2001.
[9] The United States Pharmacopeial Convention: USP39–NF34, 2016.
[10] Food and Drug Administration (FDA), USP Monograph Modernization Program. [http://www.fda.gov/Drugs/ResourcesForYou/industry/ucm357661.htm].
[11] The United States Pharmacopeial Convention, Harmonization – Pharmacopeial Discussion Group. [http://www.usp.org/usp-nf/monograph-modernization].
[12] The United States Pharmacopeial Convention, Key Issue: Monograph Modernization. [http://www.usp.org/usp-nf/key-issues/monograph-modernization],
[13] L.M. Santos, B. Davani, C.M. Anthony, et al., USP monograph modernization initiative, Am. Pharm. Rev. 18 (2015).
[14] Pharmacopoeial Forum 40(3), Organic Impurities in Drug Substances and Drug Products, 2015.
[15] [http://www.usp.org/usp-nf/development-process/monograph-modernization].
[16] USP39–NF34, Metoprolol tartrate and hydrochlorothiazide tablets monograph.
[17] USP39–NF34, Metoprolol tartrate injection monograph.
[18] USP39–NF34, Hydrochlorothiazide monograph.
[19] USP39–NF34, Hydrochlorothiazide tablets monograph.
[20] USP39–NF34, Hydrochlorothiazide capsules monograph.
[21] USP39–NF34, Metoprolol tartrate monograph.
[22] S. Bhadresh V, H.A. Raj, S. Rajanit, et al., Analytical techniques for determination of hydrochlorothiazide and its combinations: a review, Int. J. Adv. Sci. Res. 1 (2015) 114–128.
[23] J. Lu, Y. Wei, A.M. Rustum, A stability-indicating reversed-phase high performance chromatography method for simultaneous assay of two corticosteroids and estimate of their related compounds in a pharmaceutical injectable formulation, Chromatogr. A 1217 (2010) 6932–6941.
[24] J. Vojta, P. Hanzlík, A. Jedlička, et al., Separation and determination of impurities in paracetamol, codeine and pethidine in the presence of fenproporezivum in combined suppository dosage form, J. Pharm. Biomed. Anal. 102 (2015) 85–92.
[25] M.R. Nath, M. Saira, Synthesis, isolation, and characterization of hydrochlorothiazide dimer impurity, Int. J. Pharm. Pharm. Sci. 5 (2013) 867–871.
[26] Pharmacopoeial forum 41(1), In-Process Revision: Metoprolol Fumarate, 2016.
[27] Pharmacopoeial forum 41(1), In-Process Revision: Metoprolol Succinate Extended-Release Tablets, 2016.
[28] Pharmacopoeial forum 42(1), In-Process Revision: Metoprolol Tartrate Injection, 2016.
[29] H. Guan, H. Wang, D. Huang, et al., Enantioselective oxsulfanylation and oxyselenylation of olefins catalyzed by chiral Bnestr ketted acids, Tetrahedron 68 (2012) 2728–2735.
[30] Z. Chen, J. Wei, W. Li, et al., (+)-Tartaric acid-catalyzed high regio- and stereoselective amination of olefins, Chin. J. Chem. 29 (2011) 1693–1699.
[31] T. Yamana, Y. Mizukami, F. Ichimura, Studies on the stability of drugs, 13. Stability of benzothiadiazine. (5). Degradation mechanism of chlorothiazide in alkaline solution. (supplement), Yakugaku Zasshi 85 (1965) 643–655.
[32] T. Yamana, Y. Mizukami, Yakugaku Zasshi, Studies on the stability of drugs. XV. Stability of benzothiadiazines. (7). kinetics of the degradation of chlorothiazide in acidic solution, Yakugaku Zasshi 87 (1967) 1304–1308.
[33] M. Kuruma, D.K. Singh, S. Taniwara, et al., Stability behavior of antiretroviral drugs and their combinations, 3: characterization of interaction products of emtricitabine and tenofovir disoproxil fumarate by mass spectrometry, J. Pharm. Biomed. Anal. 128 (2016) 438–446.
[34] F.J. Marsac, A.C. Rumonord, D.E. Nivens, et al., Effect of temperature and moisture on the miscibility of amorphous dispersions of felinepe and poly (vinyl pyrrolidone), J. Pharm. Sci. 99 (2010) 169–185.
[35] British Pharmacopeia, Metoprolot tartrate tablets monograph, 2016.
[36] British Pharmacopeia, Metoprolol injection monograph, 2016.
[37] British Pharmacopoeia, Prolonged-release metoprolot tartrate tablets monograph, 2016.
[38] USP39–NF34, General Chapter <1086> Impurities in Drug Substances and Drug Products.
[39] Pharmacopoeial forum 42(4), In-Process Revision: Metoprolol Tartrate and Hydrochlorothiazide Tablets, 2016.
[40] USP41–NF36, Metoprolol tartrate and hydrochlorothiazide tablets monograph.

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