Macedonian pharmaceutical bulletin, 69 (Suppl 1) 255 - 256 (2023)
Online ISSN 1857 - 8969
DOI: 10.33320/maced.pharm.bull.2023.69.03.125
Short communication

Analytical strategy for discrimination between different origins of Metformin film-coated tablets

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Introduction

Many strategies are being reported to combat the occurrence of substandard and falsified medicines (Bakker-'t Hart, Ohana, Venhuis, 2021; Sweileh, 2021). Determination of characteristic analytical profile (i.e fingerprints) in combination with pattern recognition models can allow differentiation between samples by origin (manufacturer or location), authentication of suspicious samples, and successful detection of falsified samples (Been et al. 2011; Custers et al., 2016; Dégardin et al., 2016, Henrique, Scafia & Pasquini, 2001, Mazivila & Olivieri, 2018; Rebiere et al. 2017). Such fingerprints can reveal information on the manufacturing process, as well as the distribution history of the medicines.

Even though technological development provides many smart algorithm-based systems that can help in revealing the hidden differences among set of similar samples, the problem of falsification is still very present and pose huge healthcare, as well as regulatory problem (Roth, Biggs & Bempong, 2019). The forgers expect and often find a way around the approved quality specification of the medicine. The pipeline for successful prevention of the occurrence of falsified medicines on a market is restricted resources for testing outside the specification requirements (Hamilton et al. 2016).

Therefore, it is crucial to select the samples with suspicion to be falsified, based on critical risk factors, like: patient safety, number of suppliers and regulatory background, possibility of drug shortages, current regulatory requirements, etc.

For such medicines, a comprehensive strategy to reveal their origin must be anticipated. There should be elaborated background research to reveal the possible discriminatory analytical features, which will enable the differentiation between authentic and suspect-full falsification.

The aim of the research was elaborate on the discriminatory strength of the proposed comprehensive analytical methodology for the differentiation of the origin of samples with high-risk scores for the occurrence of falsification in the Republic of Kosovo**.**

Materials and methods

The selection of samples was based on a risk-based analysis of the possibility of falsification in the R. Kosovo. Film-coated tablets containing Metformin hydrochloride were identified as target finished dosage form with high-risk score for falsification based on the following most significant factors: product typically used for the long-term treatment of chronic diseases (widely used in the treatment of non-insulin-dependent diabetes mellitus, NIDDM), large distribution volume (multiple manufacturers registered for a single medicinal product) and inherent difficulties in the testing methodology (potential presence of toxic impurities).

A review of scientific literature in this area of interest and the current status of the scientific community (using key words: 'metformin', 'falsification', 'chemometrics' at Scopus database, visited June 2023) revealed no clear advances in analytical methodology to combat the possible falsification of these products.

The choice of proposed analytical (Fourier-transformed mid-range infrared spectroscopy, FTIR; Near-infrared spectroscopy, NIR & Raman spectra, LC impurity profile, and dissolution profile) and chemometric solutions (pattern recognition models developed on SIMCA

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software) were done based on the initial results and previous experience in similar projects.

Results and discussion

The classic quality control approach toward compliance testing of finished dosage forms is not discriminatory to detect possible different sample origins. Therefore, by applying a broader analytical window, valuable information on manufacturing and distribution history can be obtained. This approach includes powerful techniques, among which the non-destructive techniques are the most desirable ones. This explains the renaissance of vibrational spectroscopy in combination with chemometric tools for revealing the patterns of occurrence of small, but characteristic, analytical features around which a clustering model can be built.

Considering the above stated, several techniques were proposed for the detection of possible artifacts of different manufacturing and/or distribution history of the selected samples. Vibrational spectroscopy includes several different techniques, the most important of which are mid-infrared (IR), near-IR, and Raman spectroscopy. Combined records from these complementary techniques explain completely the vibrational modes of the formulation, in its powdered and final dosage form.

The insight into the bioequivalence characteristics among the different sets of finished dosage forms would be gained via a comparative study of dissolution profiles. The method described in the USP monograph on Metformin film-coated tablets is used for the determination of the curves of API release from the tablets, during conducting the dissolution test by sampling on several time points (5 min, 10 min, 15 min, 30 min, 45 min, 60 min).

Finally, a comparison of chromatographic impurity profiles between different batches would reflect on the possible difference on inherent stability of the APIs used during the manufacturing process, as well as an indication on stability issues from different manufacturers of metformin film-coated tablets. For this part of the study, the USP method described for the impurity testing in the monograph of Metformin tablets will be used.

Pattern recognition models build around the data from each individual technique proposed for this research, as well as combined data sets from different techniques, might be able to differentiate the origin of the selected samples.

Conclusion

The results from this research are rich in information on the characterization of the selected dosage form, thus providing improvement of the strategy for distinguishing between samples by identifying their origin and detecting possible falsification. It adds valuable support to the development of a general risk assessment tool for a sentinel market surveillance program with a focus on medicines of high public health interest. Enclosed scientific discussion empowers the rational market surveillance testing to determine the quality, but also the authenticity and sources, of the materials tested by different measures, such as the application of fingerprint techniques.

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