Macedonian pharmaceutical bulletin, 68 (Suppl 1) 235 - 236 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.112
Short communication

Root cause analysis regarding formation of N-nitrosodimethylamine impurity in drug product containing API with reactive amines

Monika Koviloska*, Katerina Tnokovska, Packa Antovska, Jelena Lazova

Research & Development, ALKALOID AD, Blvd. Aleksandar Makedonski 12, 1000 Skopje, R. N. Macedonia

Introduction

N-nitrosamines, refer to any molecule containing the nitroso functional group. The EU authorities in June 2018 became aware of the presence of a nitrosamine, N-nitrosodimethylamine (NDMA), in valsartan, blood pressure medicine belonging to a group of medicines known as "sartans". Subsequently another nitrosamine, N-nitrosodiethylamine (NDEA), was detected and other sartans were later implicated. NDMA and NDEA are considered as human carcinogens on the basis of animal studies (EMA, 2019).

Nitrosamines come from chemical reactions and can be formed in drugs during manufacturing process under certain processing conditions and in the presence of some types of raw materials, starting materials and intermediates. The formation of nitrosamines is generally only possible when secondary or tertiary amines react with nitrite or other nitrogenous agents with the nitrogen in +3 oxidation state under acidic pH (EMA, 2019). In response to nitrosamines present in pharmaceutical products, the European Medical Agency (EMA) and EU national competent authorities have published requirements and limits related to nitrosamines impurities. The manufacturers are requested to assess the risk of nitrosamine formation or presence during manufacture of human medicines and where necessary to improve their manufacturing process to prevent or limit the presence of these impurities (CMDh, 2019). The aim of this study was to determinate the root cause of NDMA formation during manufacturing of immediate release film-coated tablets, to identify the potential influence of the excipients and the technological process on the formation of the nitrosamines impurities in pharmaceutical drug product containing API which belongs to class of biguanidines, with reactive amines in the structure.

Materials and methods

In order to identify the manufacturing processing step where formation of NDMA is possible to occur, laboratory trial that simulate the manufacturing process has been manufactured. The film-coated tablets are manufactured using wet granulation technology. In the first phase, the API is mixed with the binder, povidone and then granulated with purified water as granulating aid in a high shear mixer. The wet mass obtained from granulation was passed through a suitable screen. The drying phase of the granules is performed in a fluid bed granulator. The obtained dry granulate has been passed through a suitable screen and then blended extra-granularly with the disintegrant – sodium starch glycolate and lubricated with magnesium stearate. The final blend is compressed on a tableting machine fitted with punches and dies of the required shape and size into tablet cores with defined in process physical characteristics and then film coated with the previously prepared film coating suspension. Afterwards, the film-coated tablets have been packed in primary packaging composed of PVC-Alu foil. Sampling after each phase of the production process has been performed. Further, in order to investigate if the API is a source of nitrosamines, it has been performed analysis for presence of NDMA in unstressed and stressed (at 40º/75% RH for 30 days) samples of the API. Additionally, since literature data has suggested that sodium starch glycolate can carry trace amounts of nitrites that can potentially cause formation of nitrosamines (Wu et al., 2011) and taking into consideration the proposed mechanism of formation of

*mkoviloska@alkaloid.com.mk

nitrosamines, binary mixture of the API and sodium starch glycolate has been prepared and analyzed for NDMA. Unstressed and stressed samples (at 40º/75% RH for 30 days) were analyzed. According to the literature data the other excipients present in the formulation have very low amounts of nitrites, the reason why binary mixtures with other excipients have not been prepared. Due to the highly evaporating nature of the NDMA impurity all of the samples from phase analysis (except the samples of tablet cores and film coated tablets), the binary mixture and the API were placed in screw cap glass vials with septum. Furthermore, NDMA impurities has been reported that are formed by reaction of nitrocellulose in the lidding foils with amines containing printing ink and transferred to the finished product during heat sealing blistering process via vaporization and condensation on the finished product (EMA, 2020). Although during sealing process temperatures of 180 °C or more are applied to the outside, time period of sealing is very short, normally less than one second. In addition, aluminum foil represents an absolute migration barrier and as soon as the lidding foil is sealed onto the blister material a migration of substances through the foil is not possible anymore and formation of nitrosamines is not expected during the packaging process. Therefore, despite the phase analysis several batches of finished drug product were analyzed. Samples of the finished drug product under stability studies (25ºC/60% RH), packed in the primary packaging (PVC-blanco Alu foils) immediately after production and samples packed in the primary packaging before analysis have been analyzed in order to assess the possibility for formation of the nitrosamines during the primary packaging process. The analysis of the samples has been performed by contract laboratory using LC-MS/MS method (Acquity H-class® UPLC system).

Results and discussion

Presence of nitrosamines in the analyzed API samples (stressed and unstressed) has not been detected, which indicate that NDMA impurity is not present in the API. NDMA has not been detected in the binary mixture of the API and sodium starch glycolate as disintegrant, either. Although according to the proposed mechanism of formation of NDMA and the literature data for presence of nitrite in trace in sodium starch glycolate is likely to occur (Wu et al., 2011) the results has shown that in the samples of the binary mixtures NDMA has not been detected. The results obtained from the phase analysis of the laboratory trial confirmed the result from the binary mixture, sodium starch glycolate added extra-granular have no impact on NDMA formation.

From the obtained results of the phase analysis of the laboratory trial, the presence of NDMA has been confirmed only in the sample from wet granulation processing step. The obtained results are below limit of quantification (LOQ) 0.025 ppm. The method range was 0.025 – 1 ppm. Current calculated LOQ of the used LC-MS/MS system was about 0.014 ppm. NDMA has not been detected in the other samples of the production process. Having in mind the mechanism of formation of nitrosamines, the detected NDMA in the sample of wet granulation phase indicates that the potential cause for formation of nitrosamines could be the reactive amines from the API under certain processing conditions. Due to the higher temperature in the following phases and considering that NDMA is a volatile compound in the next following phases NDMA has not been detected. However, in addition to the initial analysis it is necessary during stability to further monitor and analyze the parameter nitrosamines in the film–coated tablets of the prepared laboratory trial. Regarding the formation of the nitrosamines during the primary packaging process the obtained results from the analyzed samples have shown that the formation of nitrosamines is not likely to occur in this phase of the production process. All obtained results are either below the limit of quantification (LOQ) or just slightly above it (for one batch), regardless of the time of packaging and exposure to the primary packaging material.

Conclusion

The phase analysis has shown that the formation of NDMA can occur during the wet granulation process which implicates that several factors influence on the NDMA formation in the finished drug product that contain reactive amines in its structure. Certain conditions under which is performing the wet granulation process - humidity, heat, presence of the trace amounts of nitrites in the excipients could be the key factors for formation of NDMA. The samples form the laboratory trial would be further monitor during stability studies to assess the kinetics of formation of nitrosamines impurities.

References

CMDh/404/2019 ”Information on nitrosamines for marketing authorization holders”, September 2019.

EMA/189634/2019 “Information on nitrosamines for marketing authorization holders”, September 2019.

EMA/369136/2020 Assessment report, Nitrosamines impurities in human medicinal products.

Wu, Y., Levons, J., Narang, A., Raghavan, K., Rao, V., 2011. Reactive Impurities in Excipients: Profiling, Identification and Mitigation of Drug–Excipient Incompatibility. AAPS PharmSciTech. 12(4), 1248-1263.