HYBRID PROCESS FOR GENOTOXICS REMOVAL FROM ACTIVE PHARMACEUTICAL INGREDIENTS COMBINING ORGANIC SOLVENT NANOFILTRATION WITH POLYBENZIMIDAZOLE ADSORBENTS

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Active pharmaceutical ingredients (APIs), as most of medicines, are obtained through chemical synthesis, using highly reactive reagents and usually, low levels of reagents, fractions of catalysts, or by-products are present in the final API or drug product as impurities. Some of these impurities have unwanted toxicities, including genotoxicity and carcinogenicity, and therefore related API administration risks for patient's health has become an increasing concern of pharmaceutical companies, regulatory authorities, patients and doctors. European Medicines Agency (EMA) was the first agency to implement guidelines to control genotoxic impurities (GTIs), followed by the Food and Drug Administration (FDA). Both authorities agreed on setting as "Threshold of Toxicological Concern" (TTC) a limit at 1.5 micrograms per day for known and potential carcinogens [1,2]. Herein we report an approach based on the thermal treatment of a polybenzimidazole polymer providing novel adsorbent properties for genotoxic removal to purify API post-reaction streams. These novel adsorbents were tested for GTIs, such as methyl *p*-toluenesulfonate, *p*-toluenesulfonic acid, 4,4-dimethylamino pyridine and ethanesulfonyl chloride, from API solutions of Mometasone furoate (Meta). The current work will present a strategy of a hybrid process combining organic solvent nanofiltration (OSN) of API post-reaction streams with the adsorbers studied. The aim to include an adsorber stage, after the OSN operation, is to polish the retentate API solution for further purification or/and recovery of API lost through the permeate stream. Results will illustrate process efficiency gains.

References

[1] Teasdale A.; Elder D.; Chang S. J.; Wang S.; Thompson R.; Benz N.; Flores I. H. S., *Org. Process Res. Dev.* 17, 2013, 221-230.
[2] EMEA Guidelines on the "Limits on Genotoxic Impurities", EMEA/CHMP/QWP/251344/2006, 2006.

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