NANYANG TECHNOLOGICAL UNIVERSITY SINGAPORE | Graduate College

1. Mitigating *N*-Nitrosamine Formation in Drugs with Vulnerable Amines by Co-Crystallization with Nitrite Scavengers and Antioxidants

Date Posted	10 December 2025	
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Project Description (200-300 words)	A widely prescribed drug, ranitidine hydrochloride, was globally recalled in 2019 due to concerns over the presence of a probable human carcinogen *N*-Nitrosamine (NS) impurities. Contaminations of other drug substances (e.g., valsartan, metformin, nizatidine) with NS impurities have also been reported. NS impurities are formed by reactions between vulnerable amines of the drug substance (DS) and nitrosating agents, which typically originate from nitrite impurities present in the raw materials used in DS/drug product (DP) production (e.g., solvents, excipients). Current mitigation strategies for NS formation rely on adding nitrite scavengers and/or antioxidants in the tableting step. The current strategy's effectiveness hinges on NS inhibitors being always available in the vicinity of the DS and at high enough concentration, which is certainly not a given. To overcome this limitation, this project aims to incorporate the NS inhibitors into the drug crystals themselves via their co-crystallization. This approach ensures co-existence of the NS inhibitors and drug substance at the molecular level. Molecular structure-based screening of various NS inhibitors in terms of their co-crystallization propensity with the model drug will first be carried out. Co-crystals of the promising NS inhibitors will be prepared by either liquid-assisted grinding or solvent evaporation. The co-crystals will be incorporated into DP after which their NS inhibition effectiveness will be evaluated.	
Program/Center Website(s)	NA	
Additional Information (e.g., files with project details)	NA	