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Conclusion

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Impurity is any component that is not a chemical entity defined as the drug substance or an excipient in the drug product. Thus safety of drug product directly depends upon the quality of the pharmaceutical as presence of impurity may cause some health problems. Thus controlling the impurities in drug substance as well as drug product is utmost important. A number of impurities can be formed due to degradation on storage. Hence it is necessary to conduct stability studies to predict, evaluate and ensure drug product safety. Forced degradation study is one of the most important parameter in stability study where drug substance and drug product is exposed to various exaggerated conditions of temperature, humidity and light to predict the potential impurities that can be produced by degradation reaction, degradation pathways and intrinsic stability of the drug molecule.

In this project we have tried to identify the fundamental origin of the impurities i.e. the impurity arises due to chemical process during the synthesis of active ingredient, degradation product of API or generated due to drug- excipient interaction in drug product. This helped us to optimize the synthetic process for effective removal of process s related impurities in case of PMCR 242. Forced degradation study on all four drugs allowed us to better understand the susceptibility of drugs under various stress conditions, the potential degradation products and the degradation pathway.

Stress degradation studies performed on the drugs revealed the stability of the drugs to various stress conditions which will be very helpful in maintaining appropriate storage conditions. Doxofylline was found more susceptible to base hydrolysis than acid hydrolysis and was stable to other stress conditions. Two degradation products formed one in acid and other in base hydrolysis have been characterized and the structures are as shown below.
Thus from the structures above it is concluded that dioxalane ring of doxofylline is susceptible to acid attack causing ring opening and formation of diols while in case of base hydrolysis purine ring opens resulting in formation carboxamide product.

The second drug on which stress degradation study performed was irbesartan. Only one degradation product formed under base hydrolysis was isolated and thoroughly characterized. These preliminary findings were presented earlier during Indian Pharmaceutical Congress (IPC) 2009. Ravi Shah et al (2010) reported the formation of (1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methylamino)pentylideneamino)cyclopentane carboxylic acid (DP-II). The structure of DP-I in our study was similar to the structure of DP-II in their study (Fig 8.2).

Quantitatively this common degradation product was 30% in our work and 51.4% in work reported by Ravi Shah et al, which may be because of stronger alkaline conditions (2N NaOH v/s 0.01 N NaOH used in our study) and prolonged duration of exposure at this condition (48hrs v/s 6hr in our study).
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Trandolapril was found unstable under basic conditions and gave one degradation product and in acid hydrolysis in which two major degradation products formed (Fig 8.3). In neutral pH condition one minor degradation product formed. One degradation product (DP-II) was common in all hydrolytic conditions. The drug was found stable in all other stress conditions.

![Fig 8.3 Structures of DP-I and DP-II of trandolapril](image)

Stress degradation study of PMCR 242 revealed that it is unstable in both acid and alkali condition generating common degradation product and was found stable in other stress conditions. Mass and fragmentation pattern (MS²) revealed the possible structure as shown below

![Fig 8.4 Degradation product of PMCR 242](image)

Stress study was also performed on marketed formulations and compared with that of drug to check the drug-excipient interaction. The study revealed that there is no other degradation product generated hence the excipients are compatible with the drug.

The mechanistic pathway for the formation of all these degradation products was established. A stability indicating methods were developed and validated for the purpose of accurately quantifying the drugs in presence of potential degradation products.
Synthesis of PMCR 242 was done to identify the process related impurities. Total four process related impurities were identified and isolated for its structure elucidation. The structures were confirmed from various spectroscopic data and the origin of the impurity has been identified. The structures are as shown below Fig 8.5.

Retention times and mass spectra of IP-I and IP-III were similar to the starting material used in the final step of synthesis of PMCR 242. It indicates that some amount of starting material remained unreacted in the final compound.

Based on all spectroscopic data structures of IP-II and IP-IV have been elucidated as shown Fig 8.5. The plausible mechanism of formation of this impurity indicates that the release of morpholine during final step attacks on electron deficient carbonyl carbon of acetophenone group of PMCR 242 giving rise to IP-II. This reaction enhanced by in situ generation of HCl. So use of any basic compound like triethylamine in the final step will neutralize the HCl generated and thus protecting of carbonyl function, reducing chances of formation of IP-II.

For IP-IV all spectroscopic data were quite similar to that of PMCR 242. As the retention time was different the possibility of polymorph was ruled out. $^1$H-NMR confirms the structure having 3-acetyl pyridine moiety instead of 4-acetyl pyridine which is present in PMCR 242. When we traced the origin of the impurity it was found that the starting material 4-acetyl pyridine used for synthesis was containing 3-acetyl pyridine as an impurity giving IP-IV. When we synthesized again PMCR 242 using pure 4-acetyl pyridine (Sigma-Aldrich) the peak of IP-IV disappeared confirming the source of impurity from starting material itself.

In the future prospect the genotoxicity and carcinogenicity of the degradation products and process related impurities can be determined by in silico methods by computational software.
as these techniques are easy and cost effective when compared to that of bioassays. In these experiments if it is found to be toxic then in vivo toxicity can be performed by Ames test or chromosomal aberration test.