Chapter 2

Rational and Objective of present work

Page no. 26 to 30
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2.1. Importance of Impurity Profiling

There is an ever growing interest of scientific community in impurities present in API’s. Recently, not only purity profile but also impurity profile has become essential as per various regulatory requirements. The presence of these impurities, even in small amount, may influence the efficacy and safety of the pharmaceutical products. That is the reason why the different Pharmacopoeias, such as the British Pharmacopoeia (BP), United States Pharmacopeia (USP), and Indian Pharmacopoeia (IP) are slowly incorporating limits to allowable levels of impurities present in the API’s or formulations [31].

The impurities could arise in any synthetic step resulted in process related impurity. Impurities could arise due to degradation during storage or due to drug-excipient interaction during manufacturing. Following are the few cases where the drug was withdrawn due to toxicity.

Process-related impurities are generated at any stage of the synthetic steps. Nelfinavir mesylate is a potent and selective human immunodeficiency virus 1 (HIV-1) protease inhibitor. VIRACEPT® (nelfinavir mesylate) is manufactured by Pfizer. But in June 2007 the company had to withdraw this drug from European Union market because excess levels of ethyl methanesulfonate (EMS), a process related impurity was detected in active pharmaceutical ingredient of Viracept [32].

EMS is a potential human carcinogen. Data from animal studies indicate EMS is teratogenic, mutagenic and carcinogenic [33]. The structures of Nelfinavir and its process related impurity is as shown in Fig. 2.1.
Many drugs are known to degrade under certain conditions and the degraded products often decrease the efficacy of the drug or may cause adverse effects. Let us take an example where degradation related impurity play an important role as in pethidine.

Pethidine is a phenyl-piperidinic synthetic drug, used in the management of moderate to severe pain. Pethidine, ethyl1-methyl-4-phenyl-piperidin-4-carboxylate, is a predominantly \( \mu \)-receptor agonist. The pharmacological effects of pethidine are similar to those of morphine, but generally pethidine produces less constipation and urinary retention [34]. But in recent year use of pethidine is diminished because of the toxicity of one of its metabolite, N-methyl-4-phenyl-1, 2, 3, 6 tetrahydropyridine (MPTP), a synthetic substance deriving from hydrolytic degradation of an ester group [35].

MPTP is a very toxic compound, implicated as the cause of severe and irreversible Parkinsonian symptoms. This impurity causes selective loss of cells in the pars compacta of the substantia nigra and severe reductions in the concentrations of dopamine, noradrenaline and serotonin in the striatum. The destruction of nigrostriatal dopamine neurons, leads to symptoms that closely resemble to those present in humans idiopathic Parkinson’s disease [36]. The structures of pethidine and its hydrolytic degradation product MPTP is as shown in Fig. 2.2.
Impurities in drug product may also occur due to excipients used during formulation as drug substance is subjected to variety of stress conditions. Duloxetine hydrochloride, an antidepressant drug is unstable in acidic solution hence its enteric coated formulation was prepared using hydroxypropyl methylcellulose acetate succinate (HPMCAS) [37]. But this polymer reacts with drug forming Duloxetine succinamide impurity (Fig 2.3).

Therefore it is very important to characterize each impurity generated during synthetic process, during storage or during formulation due to drug-excipient interaction. After knowing the structure we will able to isolate the cause of formation of the impurity and can
control it to a low limit that will not affect purity, safety and potency of formulated product. Thus the importance of impurity profiling can be summarized as follows

- By identifying the structures of impurities the organic chemist can change the process or reaction conditions such that the generation of the impurity can be avoided and if not possible, can be reduced to an acceptable level.

- The characterized impurity synthesized or isolated, can be used as an impurity standard and used in quality control testing of every batch.

- These impurities can be subjected to toxicological studies in order to prove the biological safety of the drug.

### 2.2. Selection of the drugs

Cardiovascular disease (CVD) is the world's leading killer, accounting for 16.7 million or 29.2 per cent of total global deaths in 2003. In India in the past five decades, rates of coronary disease among urban populations have risen from 4 per cent to 11 per cent. The World Health Organization (WHO) estimates that 60 per cent of the world's cardiac patients will be Indian by 2015 [38]. If these looming threats of escalating epidemics of CVD are neglected, the adverse effects on development are likely to be unaffordable for a country that is now on the fast track for economic development and aspires to be a major economic power in the 21st century. Cardiovascular therapeutics forms a central part of the global pharmaceutical market, with a wide range of treatments, including leading blockbusters. For cardiovascular disorders people has to take drugs for rest of life or for longer period of time. Hence presence of traces of toxic impurities may cause problem to human health. Thus by identifying and characterizing the impurities and by performing toxicological study, we will able to reduce the risk caused by impurities.

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. However, chronic inflammation has been found to mediate a wide variety of diseases, including cardiovascular diseases, diabetes, arthritis, alzheimer’s disease, pulmonary diseases, and autoimmune
Chapter 2

Rational and objective of present work

Diseases, and even cancer. There is a direct link between inflammation and cancer. Chronic inflammation contributes to about 1 in 4 of all cancer cases [39]. TNF-α and IL-6 are some of the major mediators of inflammation which activates other mediators like interleukins, VEGF, cytokines. The expression of all these mediators is regulated by transcription factors NF-κB and AP-1 which can be induced by presence of carcinogens. So it is important to control any carcinogenic impurity in anti-inflammatory drugs.

There are many drugs and their formulations which are widely used in different disease conditions. We have selected two drugs from cardiovascular disorder (Irbesartan, trandolapril) and two drugs effective against inflammation (doxofylline, PMCR 242) as there has no reports of characterization of degradation products formed under stress degradation conditions.

2.3. Objective of the present work

The main objectives of the work is outlined as follows:

- Identify process related impurities in active pharmaceutical ingredient.
- Perform stress degradation studies to check stability of active pharmaceutical Ingredient as per ICH guidelines.
- Perform stress degradation study in drug product to identify impurities generating due to degradation of drug and drug-excipients interactions.
- Isolation of any process related impurity and/or major degradation product.
- Characterization of impurities or degradation products using various spectroscopic techniques.
- Postulate the degradation pathway and plausible mechanism of formation.
- Development and validation of stability indicating method.