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Pharmaceutical Impurities- A Mini-Review

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ABSTRACT The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. In this review, a description of different types and origins of impurities in relation to ICH guidelines and, degradation routes, including specific examples, are presented. The article further discusses measures regarding the control of impurities in pharmaceuticals.

Key Words: Bulk drugs, impurities, formulation, drug stability, degradation.

INTRODUCTION

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (ie, the identity as well as the quantity of impurity in the pharmaceuticals), is now getting receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP), are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations.

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Also, the International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances [1], products [2], and residual solvents [3]. In addition, Ahuja [4] and Gorog [5] have published books covering different aspects of impurities, including the governmental regulations and guidelines and the identification and monitoring of impurities found in drug products. There is a significant demand for the impurity-reference standards along with and the API reference standards to for both regulatory authorities and pharmaceutical companies. Interestingly, a company dealing with only impurity-reference standards, named Mikromol GmbH (Luckenwalde, Germany), has started marketing impurities found in pharmaceuticals through Promochem Group (Wesel, Germany).

A number of recent articles [6-8] have described a designed approach and guidance for isolating and identifying process-related impurities and degradation products using mass spectrometry, Nuclear Magnetic Resonance (NMR), high-performance liquid chromatography (HPLC), Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS), and tandem mass spectrometry for pharmaceutical substances.

In general, according to ICH guidelines on impurities in new drug products [2], identification of impurities below the 0.1% level is not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic. In all cases, impurities should be qualified. If data are not available to qualify the proposed specification level of an impurity, studies to obtain such data may be needed (when the usual qualification threshold limits given below are exceeded). According to ICH, the maximum daily dose qualification threshold is considered as follows:

≤ 2g/day 0. 1 % or 1 mg per day intake (whichever is lower)

≥ 2g/day 0.05%

This paper reviews the impurities found in the pharmaceuticals-identifying different sources, as well as providing examples and demonstrating possible measures to take care of the impurities in the pharmaceuticals.

SOURCES OF IMPURITIES IN MEDICINES

Medicines are the formulated forms of active pharmaceutical ingredients. There are 2 types of impurities in medicines: (1) Impurities associated with active pharmaceutical ingredients and (2) Impurities that are created during formulation and or with aging or that are related to the formulated forms.

Impurities associated in with APIs

According to ICH guidelines [1], impurities associated with APIs are classified into the following categories:

- Organic impurities (Process and Drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or non-volatile, and include the following:

Starting materials or intermediates- These are the most common impurities found in every API unless a proper care is taken in every step involved throughout the multi-step synthesis. Although the end products are always washed with solvents, there are always chances of having the residual unreacted starting materials may remain unless the manufacturers are very careful about the impurities. In paracetamol bulk, there is a limit test for p-aminophenol, which could be a starting material for some one manufacturer or be an intermediate for another.

By-products- In synthetic organic chemistry, getting a single end product with 100% yield is very rare; there is always a chance of having by-products. In the case of paracetamol bulk, diacetylated paracetamol (Figure 1) may form as a by-product.

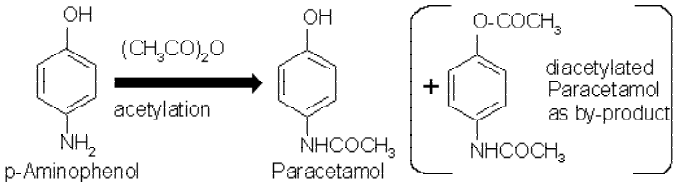
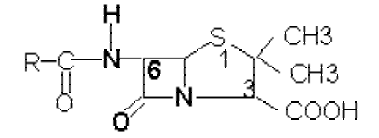


Figure 1. Production of Paracetamol from intermediate, p-Aminophenol.

Degradation products - Impurities can also be formed by degradation of the end product during manufacturing of bulk drugs. However, degradation products resulting from storage or formulation to different dosage forms or aging are common impurities in the medicines. The degradation of penicillins and cephalosporins is a well-known example of degradation products. The presence of a ß-lactam ring as well as that of an a-amino group in the C6/C7 side chain plays a critical role in their degradation [9].



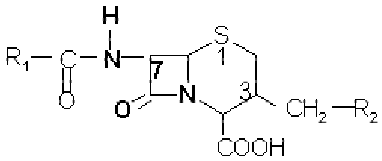


Figure 2. General Structures of (I) Penicillins and (II) Cephalosporins.

Reagents, ligands, and catalysts - These chemicals are less commonly found in APIs; however, in some cases they may pose a problem as impurities.

In general, an individual API may contain all of the above-mentioned types of organic impurities at levels varying from negligible to significant.

A detailed investigation of impurities in semi-synthetic penicillin was performed both by the manufacturers and the different research groups. A review paper on penicillins and cephalosporins [9] describes methods of isolation, detection, and quantification of degradation products, and antigenic polymeric by-products. Studies show the presence of traces of ampicillin polymers and hydrolyzed products in the API [10]. It has also been found that the presence of certain chemicals such as triethylamine has a degradative effect on the product. Ampicillin trihydrate samples having triethylamine content of 2000 ppm to 4000 ppm (determined by visual color method developed by Gist- Brocades, Delft, Holland) [10] were found to be stable under accelerated stability testing. However, the product showed appreciable degradation when triethylamine content became 7000 ppm. Recent pharmacopoeia [11] included the limit tests for the traces of impurities present in ampicillin and amoxycillin bulk raw materials. The residual solvents associated with these APIs have also been determined [10].

As the organic impurities are the most common product- as well as process-related impurities, it is the responsibility of both the manufacturers of APIs and the users (ie, formulators) to take care of these impurities according to ICH guidelines or compendia.

In addition, for an optically active single isomer drug there could be enantiomeric impurities present in the API.

Enantiomeric impurities - The single enantiomeric form of a chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile and an increased therapeutic index with a more favorable adverse

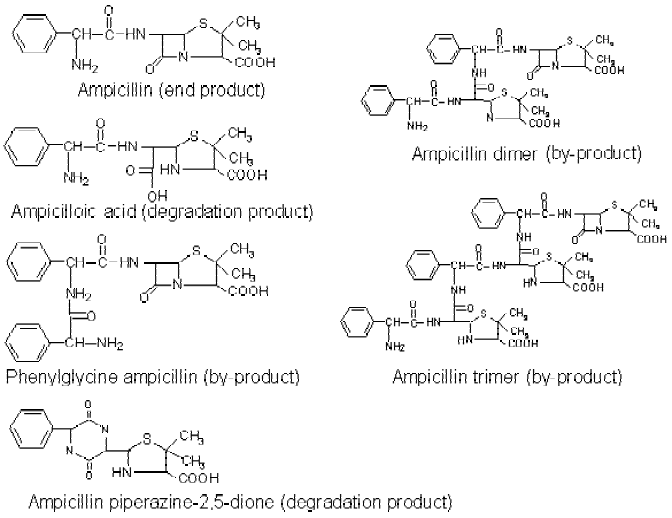


Figure 3. Structures of Ampicillin and Ampicillin-related products [10].

reaction profile [12]. However, the pharmacokinetic profile of levofloxacin (S-isomeric form) and ofloxacin (R-isomeric form) are comparable, suggesting the lack of advantages of single isomer in this regard [12]. In any case, cost benefits as well as the patient's compliance need to be considered in selecting drugs. For the manufacturers of single enantiomeric drug (eutomer), the undesirable stereoisomers in drug control are considered in the same manner as other organic impurities. The prominent single isomer drugs, which are being marketed, include levofloxacin (S-ofloxacin), levalbuterol (R-albuterol), esomeprazole (S-omeprazole).

Inorganic impurities

Inorganic impurities may also derive from the manufacturing processes used for bulk drugs. They are normally known and identified and include the following:

Reagents, ligands, and catalysts - The chances of having these impurities are rare: however, in some processes, these could create a problem unless the manufacturers take proper care during production.

Heavy metals - The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impuri-

ties of heavy metals can easily be avoided using demineralized water and glass-lined reactors.

Other materials (eg, filter aids, charcoal) - The filters or filtering aids such as centrifuge bags are routinely used in the bulk drugs manufacturing plants, and, in many cases, activated carbon is also used. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminations.

Solvent residues

Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production. It is very difficult to remove these solvents completely by the work-up process; however, efforts should be taken to the extent possible to meet the safety data. Some solvents that are known to cause toxicity should be avoided in the production of bulk drugs. Depending on the possible risk to human health, residual solvents are divided into 3 classes [3]. Solvents such as benzene (Class I, 2 ppm limit) and carbon tetrachloride (Class I, 4 ppm limit) are to be avoided. On the other hand, the most commonly used solvents such as methylene chloride (600 ppm), methanol (3000 ppm), pyridine (200 ppm), toluene (890 ppm), N,N-dimethylformamide (880 ppm), and acetonitrile (410 ppm) are of Class II. Class III solvents (acetic acid, acetone, isopropyl alcohol, butanol, ethanol, and ethyl acetate) have permitted daily exposures of 50 mg or less per day. In this regard, ICH guidelines [3] for limits should be strictly followed.

Impurities related to formulation

Apart from bulk drug-related impurities, the formulated form of API may contain impurities that form in various ways.

Impurity forms during formulation

a) method related

A known impurity, 1-(2,6-diclorophenyl)indolin-2-one is formed in the production of a parenteral

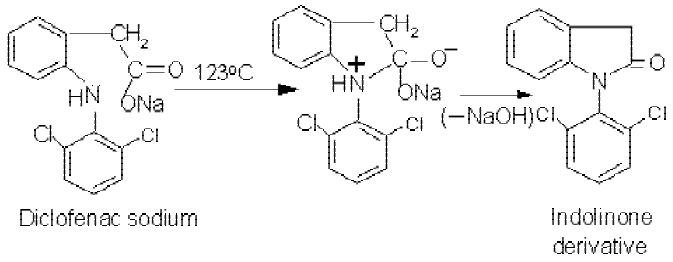


Figure 4. Formation of impurity on autoclaving of Diclofenac sodium [13].

dosage form of diclofenac sodium if it is terminally sterilized by autoclave [13]. It was the condition of the autoclave method (ie, 123 + 2°C) that enforced the intramolecular cyclic reaction of diclofenac sodium forming the indolinone derivative and sodium hydroxide. The formation of this impurity has been found to depend on the initial pH of the formulation. The concentration of the impurity in the resultant product in the ampoule exceeds the limit of the raw material in the BP.

b) environmental related

The primary environmental factors that can reduce stability include the following:

Exposures to adverse temperatures - There are many APIs that are labile to heat or tropical temperatures. For example, vitamins as drug substances are very heat -sensitive and degradation frequently leads to loss of potency in vitamin products, especially in liquid formulations.

Light-especially UV light - Several studies have reported that ergometrine as well as methyl ergometrine injection is unstable under tropical conditions such as light and heat, and a very low level of active ingredient was found in many field samples [14-16]. In only 50% of the marketed samples of ergometrine injections tested [16] did the level of active ingredient comply with the BP/USP limit of 90% to 110% of the stated content. The custom-made injection of ergometrine (0.2 mg/mL) showed almost complete degradation when kept 42 hours in direct sunlight.

Humidity- For hygroscopic products, humidity is considered detrimental to both bulk powder and formulated solid dosage forms. Aspirin and ranitidine are classical examples.

c) dosage form factors related

Although the pharmaceutical companies perform pre-formulation studies, including a stability study, before marketing the products, sometimes the dosage form factors that influence drug stability force the company to recall the product. Fluocinonide Topical Solution USP, 0.05%, (Teva Pharmaceuticals USA, Inc., Sellersville, Pennsylvania) in 60-mL bottles, was recalled in the United States because of degradation/impurities leading to sub-potency [17]. In general, liquid dosage forms are very much susceptible to both degradation and microbiological contamination. In this regard, water content, pH of the solution/suspension, compatibility of anions and cations, mutual interactions of ingredients, and the primary container are critical factors.

Microbiological growth resulting from the growth of bacteria, fungi, and yeast in a humid and warm environment may result in oral liquid products that are unusable for human consumption. Microbial contaminations may occur during the shelf life and subsequent consumer-use of a multiple-dose product due to inappropriate use of certain preservatives in the preparations [18], or because of the semi-permeable nature of primary containers.

Formation of impurities on aging

a. Mutual interaction amongst ingredients

Most vitamins are very labile and on aging they pose a problem of instability in different dosage forms [19], especially in liquid dosage forms. Degradation of vitamins such as folic acid, pantothenic acid, cyanocobalamin, and thiamine do not give toxic impurities; however, potency of active ingredients drops below pharmacopoeial specifications.

Because of mutual interaction, the presence of nicotinamide in a formulation containing 4 vitamins (nicotinamide, pyridoxine, riboflavin, and thiamine) causes the degradation of thiamine to a sub-standard level within a 1-year shelf -life of vitamin B-complex injections [20]. The marketed samples of vitamin B-complex injections were found to have a pH in the range of 2.8-4.0. The custom-made formulation in a simple distilled-water vehicle and in a typical formulated vehicle that included disodium editate and benzyl alcohol was also investigated, and similar mutual interaction causing degradation was observed.

b. Functional group- related typical degradation

Ester hydrolysis -Examples included the following: Aspirin, benzocaine, cefotaxime, cocaine echothiophate, ethyl paraben [21], cefpodoxime proxetil [22].

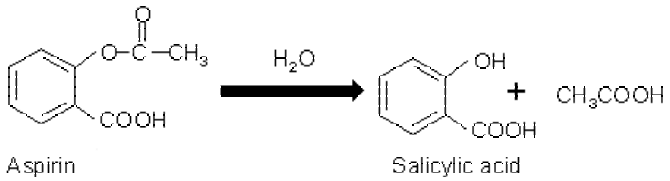


Figure 5. Formation of Salicylic acid impurity from Aspirin.

Hydrolysis- Hydrolysis is a common phenomenon for the ester type of drugs, especially in liquid dosage forms. Examples include benzylpenicillin, barbitol, chloramphenicol, chlordiazepoxide, lincomycin, and oxazepam [21].

Oxidative degradation - Hydrocortisone, methotrexate, adinazolam, hydroxyl group directly bonded to an aromatic ring (eg, phenol derivatives such as catecholamines and morphine), conjugated dienes (eg, vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes (eg, flavorings) are all susceptible to oxidative degradation.

Photolytic cleavage - Pharmaceutical products are exposed to light while being manufactured as a solid or solution, packaged, held in pharmacy shops or hospitals pending use, or held by the consumer pending use.

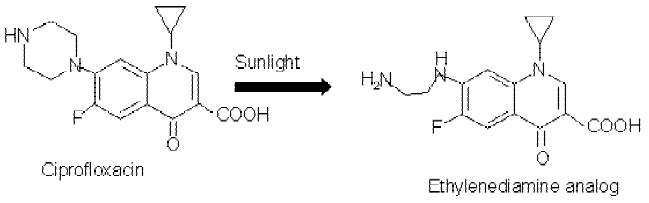


Figure 6. Photolytic cleavage of Ciprofloxacin in eye drops preparation [27].

Ergometrine [16], nifedipine [23], nitroprusside, riboflavin, and phenothiazines are very labile to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions. Most compounds will degrade as solutions when exposed to high energy UV exposure. Fluoroquinolones antibiotics are found to be susceptible to photolytic cleavage [24-28].

In ciprofloxacin eye drops preparation (0.3%), sunlight induces photocleavage reaction producing ethylenediamine analog of ciprofloxacin [27].

Decarboxylation- Some dissolved carboxylic acids, such as p-aminosalicylic acid, lose carbon dioxide from the carboxyl group when heated. Decarboxylation also occurred in the case of photoreaction of rufloxacin [28].

RECOMMENDATIONS

Critical factors regarding bulk drugs' quality

During crystallization - The size of crystals sometimes determines the quality, especially the stability, of bulk drugs. Large-size crystals can entrap a minute amount of chemicals from the mother liquor, which ultimately causes the degradation of the drug. Thus, the manufacturers of bulk drugs should take care to produce finer crystals while isolating the products.

Washing the wet cake - Washing the wet cake or powder in the centrifuge should be thorough to remove unwanted chemicals including residual solvents.

Drying- Use of a vacuum dryer or a fluid-bed dryer is always preferable to a tray dryer in the pharmaceutical bulk drug industry. The high thermal efficiencies, reduction of drying time, and more uniform drying are helpful in drying sensitive drug substances. However, if a tray dryer is used then initial airflow at ambient conditions should be considered before exposing the materials to a relatively higher fixed temperature.

Appropriate packaging

Light- sensitive pharmaceutical products need light-protective packaging. An accelerated stability testing conducted using marketed ampoules of ergometrine wrapped with either black carbon paper or aluminum foil produced negligible degradation against direct sunlight [16]. Similar use of opaque containers for ciprofloxacin eye-drop preparation can protect the active ingredient from photodegradation to some extent compared with transparent containers [27].

Use of production method based on stability studies

In finalizing the method of preparation, a detailed investigation, including stability studies, should be undertaken. In the case of parenteral preparations, aseptic filtration versus terminal autoclaving method for sterilization should be evaluated before finalizing the method. For diclofenac sodium injections, the aseptic filtration process has been recently recommended as the alternative to the autoclave method that produces impurity [13].

Measures by pharmacopoeias

It has been observed in the pharmacopoeias that there is an impurity limit shown in the specifications of certain raw materials but not given in the case of products made of those raw materials. Although the impurity limit on the drug substances is applicable to the drug products, it would be con-

venient for the users if the impurity limits were also mentioned in each dosage forms. The limits may vary from orals to injectables. Diclofenac sodium is such an example where an impurity limit is not mentioned in the case of injections. ICH recommendation [2] can be incorporated in the pharmacopeias. In addition, a generalized monograph on the impurity issues can be added in the pharmacopoeia.

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