Cancer is a disease where the body's cells grow uncontrollably and can damage the other parts of the body [1]. This cell growth can lead to either solid mass i.e., tumor or liquid mass (blood cancer or bone marrow cancer). In the world, cancer is the main cause of death for which the treatment is given in terms of cytotoxic drugs, chemotherapy and/or radiotherapy [2]. In 2007, 79 lakhs people were killed by cancer which is almost 13% of total deaths [3]. In 2018, cancer was accounted for 9.6 million deaths or one in six deaths [4]. Chemotherapy involves the use of anticancer drugs of various categories which can selectively destroy the cancer cells or at least reduce their growth [2], [5]. Although these drugs can kill the cancerous cells, they may also destroy the healthy cells of the body. Based on the mechanism of action, these anticancer agents are classified i.e., Antimetabolites, molecular targeting agents, DNA-interactive agents, hormones and other biological drugs, and anti-tubulin agents [2]. Apart from the selective targets of anticancer agents, they are highly toxic to normal body cells creating many toxic effects to the body such as bone marrow suppression, hair loss, nausea gastrointestinal lesions etc. These toxic effects again are at very high risk for the unknown impurities generated from the degradation of the anticancer drugs itself. Hence, the control of the degradation products through their identification and characterization is utmost necessary to avoid its most -toxic impacts to the body.

Regulatory authorities also expect that all the impurities of the anticancer drugs shall be targeted extensively and if impurities are found to increase above the threshold levels during drug storage, they must be identified and proved its toxicity in terms of carcinogenicity or mutagenicity.

1.1 IMPURITIES

The reason why the impurity control is the most crucial aspects considered in pharmaceutical industries as well as by regulatory authorities is simply because the impurities present in the drug substance or formulation have huge impact on the purity of drug substance or drug product. Considering this significance, strict limits of impurities are available for many years especially in various ICH guidelines and other

regulatory bodies documents. [19-20,43, 44-45]. Impurity profiling is defined the identification and characterization of all the probable impurities and degradation products present in drug substance and drug products using various spectroscopic techniques and if required development of methodology for their quantification by suitable pathway.

1.1.1 Sources of impurities:

Based on sources of impurities, they can be of following types:

1.1.1.1 Impurities generated during synthesis:

This type of impurities originates from the materials used for the synthesis of active pharmaceutical ingredients of the drug product. During organic synthesis of drug, various kinds of raw materials, starting materials, intermediates and other stage products are used which may contain many unknown impurities depending upon their synthesis. Such impurities may be observed in final drug substances synthesized, if they are not eliminated in purification step of drug. One more characteristic of synthesis impurities is that they generally do not increase with time duration or other degradation conditions applied in drug substance. They are observed, generally, at the same level when stability studies of drug are conducted even for number of years after synthesis.

1.1.1.2 Impurities generated while formulation of drug products:

Like raw materials and other starting materials in synthesis of drug substances, the excipients are used in addition to active pharmaceutical ingredients to formulate final drug products. Therefore, if any excipients contain some impurities, they may be observed in drug products. Other than this, sometime impurities may be formed by the reaction between the excipient and other excipient or even with active ingredient.

1.1.1.3 Degradation impurities:

Stability of a drug depends on environmental factors such as air, sunlight, UV light, heat and humidity applied during their storage. During initial stages, if it is observed to have some degradation products under some atmospheric conditions approaching near to acceptable limits, the storage condition of the drug products is changed accordingly so that the impurities can be reduced below threshold level and overall quality of drug can be maintained throughout its shelf life[6].

1.1.1.4 Polymorphism related impurities:

If a substance has same elemental composition but crystal forms are different, such crystal arrangements are called polymorphs and the phenomenon is called polymorphism. There is a lot of focus on the physical attributes of the drug related to the morphology of the drugs. The mixture of multiple polymorphic forms within the single crystallization procedure was observed in several instances and in some other situations the drug converts from one polymorphic form to the pseudo polymorphic form or another crystal form when stored at different storage conditions or when the drug comes in contact with different excipients and the packaging components.

Therefore, the importance of understanding the distribution pattern and also incorporation of such type of data generated by sophisticated analytical techniques like XRPD (X-Ray Powder Diffraction chromatography), DSC (Differential Scanning calorimeter), Microscopic analysis and Raman Spectroscopy into the drug applications

1.1.1.5 Stereochemistry related impurities:

Stereoisomers can be considered impurity in drug substance, although ICH excludes stereo chemical impurities, pharmacopoeias consider them as ordinary impurity. The differences in pharmacological or toxicological profiles of stereoisomers suggest that it should be monitored carefully.

Due to high importance of enantiomeric impurities analysis, it is considered as one of the hot topics of current pharmaceutical industry which is shown by many book chapters, and review chapters devoted to this area [7-10]. Sometimes, the main active drug's enantiomer found to be genotoxic in nature, hence its isolation and estimation

would become utmost important. For instance, thalidomide drug has two isomers (R) and (S) in which R-isomer is therapeutically active but S-isomer is teratogenic in nature [11-13].

1.1.2 Classification of Impurities:

The ICH and pharmacopoeias have classified the impurities as follows:

1.1.2.1 Organic impurities:

Organic impurities are either process related impurities or degradation impurities of drug. The process related impurities are impurities which arise from the various raw materials, starting materials, intermediates or solvents and other ingredients. Organic impurities observed due to degradation of drug are observed due to exposure of drug to various degradation conditions either during storage of drug or during process of drug manufacturing. The organic impurities may be volatile or non-volatile in nature.

1.1.2.1.1 Starting materials or intermediates:

The key starting materials or various stage products and intermediate substances which are used for synthesis of drug or manufacturing of drug product may be observed in drug in minor trace levels. This would happen if proper care has been taken for the purification step which is crucial last stage step in organic synthesis of drug substances where multiple washes of appropriate solvents are given to purify the compound and to remove any such trace level impurities carried forward from starting materials or intermediates.

1.1.2.1.3 Degradation products:

Other than the exposure of various materials to degradation conditions during synthesis or manufacturing, it is also observed that drug itself may get degraded during storage. Form such degradation of drug itself, many degradation products can be formed either due to aggravated conditions of oxidation, temperature, humidity and other

environmental factors. Such degradation products can be easily identified at laboratory level if they are exposed to forced degradation study under various stress conditions of heat, light, oxidation and hydrolysis. Stability studies of samples kept at various long term and short term storage conditions in stability chambers also help in identification of any degradation products generated while long term storage of drug in that particular aggravated storage conditions.

1.1.2.1.4 Reagents, other chemicals and catalysts:

Like starting materials and other active drug components, the chemicals which are not therapeutically active but are used for synthesis of drug, can also be carried over to the final drug in trace levels. The chemicals which are generally used for such synthesis are some reagents or catalysts. It becomes difficult to identify the exact source of organic impurities after observation in drug, but there are several extensive preventive ways which can utilized so that such impurities could be avoided to be carried forward to the final step of manufacturing.

1.1.2.2 Inorganic Impurities:

The inorganic compounds such as heavy metals can also be observed in drug as an impurity. The source of such impurities is mainly the stainless steel vessels used during manufacturing. There are various analytical ways by which such inorganic impurities can be identified and estimated. Residue on ignition is the test where the drug substance is ignited at very high temperature of 600°C after charring with H_2SO_4. After ignition of drug for specified time duration of 1 to 4 hours, the residue remains in the crucible are only due to inorganic impurities present in the drug. This can be estimated by gravimetric measurements of initial weight of drug and final residual weights of impurities after ignition. However, this test required large quantity of drug ranging from 1-2 g. If the drug quantity is not sufficient, inorganic content can also be quantified by indirect way with 5-10 mg of drug also. This is by measuring of percentage of carbon, hydrogen or nitrogen in CHN analyzer after combustion at very high temperature. This test would give the assay of drug based on the amount of carbon observed after

combustion and the theoretical carbon based on molecular formula. This would give the percentage of drug which are not combustible and considered as inorganic content. However, both the ways of estimation of inorganic content in drug are quantitative only not qualitative. This means that if the presence of target metals is required to be monitored, different instrument such as inductively coupled plasma spectroscopy can be used for this purpose. In this technique, the exact metals can be quantified based on standard response of the reference standard of metals used in the study. The examples of metals which can be estimated in this way are silver, platinum and lead.

1.1.2.3 Residual solvents:

The residual solvents presence is always noted in drug if various organic solvents such as methanol, acetonitrile, methylene dichloride etc. are used during synthesis of drug. All these residual solvents are volatile and toxic in nature. Hence various regulatory bodies have defined their limits in final drug which should be controlled by pharmaceutical industry. The estimation of residual solvents is generally achieved by gas chromatographic analysis where the exact content of residual solvents can be estimated by comparison with the response of respective solvent standard [14, 39]. The residual solvents are classified as class-1, class-2 and class-3 based on their toxicity levels where the class-1 solvents are considered to be most toxic hazardous to environment and class-3 are least toxic in nature.

1.1.2.3.1 Class 1

The examples of class-1 residual solvents are benzene, carbon tetrachloride etc. Because of severe toxic effects of class-2 solvents, these should be strictly avoided for manufacturing of drug substances. However, if they are unavoidable, their use is restricted and strictly monitored by gas chromatographic analysis [14].

1.1.2.3.2 Class 2

Some solvents categorized as class 2 are acetonitrile, chloroform, methanol, hexane, 1,4-dioxane, and toluene [14].

1.1.2.3.3 Class 3

Some solvents categorized as class 3 are acetic acid, acetone, isobutyl acetate, and 1-pentanol [14]. Based on the low toxicity levels of class-3, they are monitored at 0.5% level i.e., 5000 ppm.

1.2 IMPORTANCE OF IDENTIFICATION OF IMPURITIES

- In the process of developing the drug products, the potential toxicological profiles of each of the identified impurities have to be understood and its class either being genotoxic, mutagenic or in cases of organic volatile impurities (OVI) / residual solvents whether they are in the class 1, class 2 or class 3 should also be identified.
- The regulatory requirements for impurity profiling and forced or stress degradation study have been extended to generic drugs and products in recent years. Due to the stringent environment laid down by regulatory authorities, there is steady increase in product recalls from the market. One of the reasons often cited is the presence of impurities or degradation products (DPs) beyond the prescribed limits.
- The major deficiencies in the DMF's (Drug master files) and ANDA's applications submitted to agencies like USFDA and EMEA, after the review of the application are mainly revolving around the identification, reduction in levels, characterization, justification of levels, and qualification of impurities.
- This also includes the queries on the data related to the identification of the degradation pathways, illustration of the different degradation pathways, stability studies, validation of SIAMs, separation of the identified and unidentified impurities from the peaks of drug substance and between the impurities itself, the stress degradation studies under different harsh conditions and the residual solvents and the justifications of their levels.
- Having a thorough analysis of the impurity profiles of drug helps immensely in understanding the safety and efficacy of the drug substances and also helps the

pharmaceutical companies to get the approvals without any delay.

1.3 FORCED DEGRADATION STUDY:

Stress degradation analysis is quicker tool to generate the degradation products from the drug substances whereas the longer duration stability conditions required six to twelve months duration time to generate the degradation products. In this study, different stress conditions such as heat, acid hydrolysis, alkali hydrolysis, oxidation, and UV exposure are applied and generation of degradation products are observed [15-18]. Conducting forced degradation study is considered crucial as it gives useful information about the stability and shelf-life of the drug. The ICH guidelines are available for information on how to conduct the forced degradation study under each stress conditions [19-23].

1.3.1 Selection of degradation conditions:

Initially the drug substances stability can be checked under varied -pH and temperature medium as such to check if any degradation products are observed or not.

1.3.1.1 Hydrolysis:

In hydrolysis stress testing, the drug was exposed and allowed to react with water under different pH conditions ranging from acidic to alkali pH medium. Here, the concentration of acid or alkali ranges from 0.1 to 1N. The solution shall be kept at defined time period under this stress conditions. Blank solutions shall also be required to be prepared to nullify the interference from blank when final degradation chromatograms are reviewed. Also, the solution, after stress condition time period, shall be neutralized with opposite acid or alkali with the same concentration.

1.3.1.2 Oxidation:-

The drug substances require free radical initiators for oxidation process. Hydrogen peroxide is a good free radical initiator which can be used in the concentration range of 0.1% to 3.0%. The temperature can also be applied for acceleration in generation of degradation products.

1.3.1.3 Thermal

Many degradation products are found to be generated due to thermolabile nature of drugs. Generation of these degradation products can be accelerated by applying elevated temperature i.e., 40°C to 80°C for short duration of time. The solid drug substances shall be exposed to thermal degradation in both the forms of solid state and liquid solution in some diluent.

1.3.1.4 Photolytic degradation:

When the drug substances are exposed to UV or fluorescent light, they are prone to generate some degradation products through free radical oxidation process which are not generated in oxidative degradation process. UV radiation has sufficient energy to break double bonds in the structure. Due to high energy, UV light can create ionization in the structure by which electrons are removed from the structure. Due to these movement of electrons double bonds of the structures get affected which would otherwise is not possible[24]. Isomer and dimer generation are some examples of non-oxidative degradation products. The radiation range that generally applied in UV chamber for this study is between 300-800 nm.

1.4 DEVELOPMENT OF STABILITY INDICATING METHODS FOR ESTIMATION ANTICANCER DRUGS IN PRESENCE OF THEIR DEGRADATION PRODUCTS

Stability indicating methods are the analytical methods which are capable of showing stability of the drug substance or drug products. Chromatographic methods such as HPLC, HPTLC are the preferred techniques showing stability of the drug means they are capable of detecting the compound/analyte peak in presence of other interferences. These other interferences may be in terms of degradation products, excipient or other placebo components. All peaks which are prone to be generated during storage of the drug, must be well separated from the main peak. Out of the all the instrument techniques available such as TLC, HPTLC, GC and HPLC, HPLC is the extensively utilized instrument for development of stability indicating methods as it highly specific, sensitive, better resolution capacity and quantitation capacity. Non-volatile, thermo-

labile compounds or polar compounds are also easily analyzed by these techniques. Hence most of the SIAMs for various drugs are found in literature by HPLC compared to other capable instrument techniques [25-33].

The development of stability indicating methods involves first step as the determination of values of drug properties such as pKa value, solubility and wavelength maxima of the drug. Based on pKa value, the mobile phase pH value can be determined which is often kept between pKa +/-2 so that better resolution between peaks can be achieved[34]. For better elution of main peak in the initial 1/3rd region of the chromatogram, buffer is mixed with some organic solvents such as acetonitrile or methanol which helps to elute the polar peaks faster from the column and appears earlier in the chromatogram. If not sure, initially the trials can be started with the mixture of aqueous solution (buffer) and acetonitrile in the ratio of 50:50 and based on the observation, it can be optimized for better elution pattern by changing the ratio of mixture. Similarly gradient of the mobile phase run can also be optimized. Initially the gradient can be started with 0% of mobile phase B to 80-100% of mobile phase at the end of the run time. From this run, the elution of main peak can be observed and further optimized for better elution pattern in the chromatogram. So ultimately, good peak symmetry, better peak to peak resolution and good elution pattern in the chromatogram should be the main targets of the good stability indicating method. Moreover, there are also some mobile phase modifiers which can be used to retain the drug into the column. Some ion pair reagents such as octane sulphonic acid salts are examples of this. Triethylamine or trifluoroacetic acid are also used for better retention of the drug into the column [35-36].

Wavelength maxima (λmax) can be determined by running the drug solution in PDA detector of HPLC in the wavelength range between 190-400 nm. Based on the results from PDA detector, it is easy to find the wavelength where the drug is showing maximum response. Some drugs may have more than one wavelength maxima. In such cases, the wavelength maximum of main drug is compared with wavelength maxima of other degradation products. Finally appropriate wavelength should be selected by comparison of all the absorbing wavelength of drug and other interferences.

From the PDA detector, it is also possible to estimate the peak purity of the peak. Peak

purity results help in identification of any degradation products that get merged with the main peak. Many times, the degradation products are generated but get merged with the main peak and are not separated in the LC chromatogram. In such cases, the lower peak purity results were obtained suggesting the presence of other interferences peaks in the main peak.

For improving the peak shape and other peak symmetry parameters, column temperature can be applied. The uniform column temperature also helps to get uniform chromatogram in the small but deliberate varied condition of varied laboratories [37]. Moreover, if the sample solution is observed to be degraded very fast within short period of time after preparation i.e., within 1 to 12 hours, it is suggested to keep the auto-sampler temperature of the HPLC at low levels i.e., 2-8 °C. This helps to stop the degradation process of the drug while waiting for the injection in the HPLC. If low temperature of the sampler also can't stop the degradation process, freshly preparation of solutions is suggested and implemented. However, the freshly preparation of sample at the time of injection is very cumbersome for the analyst as they have to prepare the solution freshly before each and every injection of the sample in HPLC. This is more problematic when the run time is very short for example 15-20 minutes.

Selection of suitable column also plays a key role. There are multiple kinds and types of columns are available commercially from the manufacturers ranging from Waters, Phenomenex, Agilent, Thermo, Kromasil, Vydac, Chiralpak and other miscellaneous. The various types of columns include C18, C8, Phenyl, biphenyl, octadecyl silane, and other latest invented by column manufacturers. The column length and diameters also vary ranging from 50mm length column to 300mm length column. Internal diameters of the column vary in the range of 2.5 to 4.6mm. The particle sizes of the columns vary in the range of 2.5µ to 5µ size. Column dimensions and particle size have a direct impact on run time and retention time of the sample. For example, if the main drug peak elutes very faster in 150mm column, lengthier column is suggested so that the drug can be retained in the column.

Other crucial parameters are flow rate and injection volume which can be effectively used for better chromatography. If the flow rate is increased, the peaks elute faster and

appear earlier in the chromatograms. If the peak response of 100% level of the drug solution is very low at low injection volume, the injection volume can be increased based on the injection loop available in the instrument. If the peak gets overshoot in the chromatogram i.e., the peak response goes beyond the peak height of 1 AU, injection volume can be lower down to accommodate the peak height below 1 AU. This is very important as other validation parameters such as linearity and method precision would only pass if the peak response is within the appropriate range and within the capacity of detector.

1.5 DEGRADATION KINETIC STUDY OF ANTICANCER DRUGS

The exploration of stability behavior of the anticancer drugs also involved the detailed analysis of degradation products generation and increment in various specified conditions through degradation kinetic study. It is most crucial to measure the impact of temperature, concentration of solution, pH of the medium, time duration of exposure on the generation of degradation products. From the results of the statistical plot of Arrhenius equation, goodness of fit for the line (R2) and other relevant statistical parameters, it is possible to study that the degradants follow one particular order of reaction whether it is zero, first, second or pseudo first order reaction kinetics. The rate constant and activation energy can be calculated which are important to understand shelf life of the drug. Based on the order of reaction, rate constant (K) can be calculated as shown in below formula [38].

For zero order reaction: Rate constant (K)= -Slope

For first order reaction: Rate constant (K) =-2.303*Slope

For second order reaction: Rate constant (K) = Slope

For calculation of activation energy, the Arrhenius equation is required which has correlation between the rate constant and temperature of the reaction system.

$K = Ze^{-Ea/RT}$

Where Z= Geometry constant

K = Rate constant

R = Gas constant (8.314 J/mole)

T = Temperature (Kelvin)

Ln K = -Ea/R (1/T) + ln Z

Y = mx + C

Hence slope = -Ea/R from the Arrhenius plot.

Estimation of half-life:

The half-life of the reactions which follow first order is proportional to the rate constant only. Hence, the half-life of reactions following first order kinetics stays same throughout the reaction even though the reactants concentrations are reducing. On the other hand, the half-life for reactions following second order is inversely proportional to initial concentration of reactant. It means the half-life increases as the reaction time passes and initial concentration of reactant reduces.

For first order reactions: Half-life $t_{1/2}$ = ln 2/K

For second order reactions: Half-life: $t_{1/2} = 1/K[A]_0$

Where ln 2= 0.6931

$[A]_0$ is initial concentration of reactant.

1.6 ANALYSIS AND STRUCTURE ELUCIDATION OF ANTICANCER DRUGS AND ITS DEGRADATION PRODUCTS:

The analysis of active pharmaceutical ingredients of pharmaceutical formulations in presence of their degradation products or other impurities is the prime and challenging requirement of industry nowadays. For this, the separation techniques such as LC or CE coupled with UV detector have been used for last several decades [39-41]. However,

recently the most common hyphenated techniques used for this purpose is LC-MS which allows the detection very low levels of degradants in the anticancer drugs. For example, the method for estimation of oxaliplatin in presence of chloride by LC-MS /MS was published in 2004 [42]. For structure elucidation of unknown impurities, recent most advanced techniques such as NMR, HRMS, and FTIR have been found to be used in published literature. By NMR studies and experiments, it is possible to understand the proton and carbon environment of the unknown chemical compound. It is also possible to exactly identify the number of protons or carbons in the structure. LC-MS is used for getting the exact mass of the unknown compound either separated by LC or by direct infusion into MS detector. The further fragmentation pattern of the unknown compounds can also lead to exact elucidation of the structure based on exact mass values. ‘

HRMS is the orbitrap mass resolution technique, the most recent in the field of MS hyphenated techniques, which can give the exact mass of the unknown compound with better resolution and with very high sensitivity.

1.6.1 Conventional approach

The better technology has made it possible that the degradation products generated can be isolated using preparative LC or HPLC fraction collector. These collected fractions shall be concentrated and purified by freeze drying or evaporator. The concentrated isolated degradation products are then run on various instruments like LC-MS, MS/MS, NMR, and IR which can give detailed structural information; by interpreting them the structures of unknown degradation products can be postulated. However, this approach is very tedious and time consuming as it requires lot of time to collect the fractions from preparative LC or other fraction collector instrument.

1.6.2 Hyphenated methods:

The modern approach against the conventional way is the usage of hyphenated sophisticated techniques. HPLC coupled with MS detector or HPLC coupled with NMR are the examples of such techniques. Out of these two, LCMS and LC-MS/MS are extensively used in the industry to get the information of unknown degradation products based on the exact mass of the impurities observed and fragmentation mass of the same

which has been observed. This modern approach is easy and more accurate to get the correct information which can lead to correct structure elucidation of the degradation products [35].

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