IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, January 2024

An Overview on Impurity Profiling of Pharmaceutical Active Ingredients

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Abstract: *Standard list of basic laboratory safety rules are given below and must be followed in every laboratory that uses hazardous materials or processes. These basic rules provide hygiene and behaviour safety information to avoid accidents in the laboratory. Laboratory specific safety rules may be required for processes, equipment, and materials, which should be addressed by laboratory standard operating procedures (SOPs) .Basic Safety Rules: Know locations of laboratory safety showers, eyewash stations, and fire extinguishers. The safety equipment may be located in the hallway near the laboratory entrance. Know emergency exit routes. Avoid skin and eye contact with chemicals Minimize all chemical exposures. No horseplay will be tolerated. Assume that all chemicals of unknown toxicity are highly toxic*

Keywords: Pharmaceutical Active Ingredients.

I. INTRODUCTION

Laboratory Safety:

1.1 Introduction of Laboratory Safety:

Standard list of basic laboratory safety rules are given below and must be followed in every laboratory that uses hazardous materials or processes. These basic rules provide hygiene and behaviour safety information to avoid accidents in the laboratory. Laboratory specific safety rules may be required for processes, equipment, and materials, which should be addressed by laboratory standard operating procedures (SOPs) .Basic Safety Rules:Know locations of laboratory safety showers, eyewash stations, and fire extinguishers. The safety equipment may be located in the hallway near the laboratory entrance. Know emergency exit routes. Avoid skin and eye contact with chemicals Minimize all chemical exposures. No horseplay will be tolerated. Assume that all chemicals of unknown toxicity are highly toxic. Post warning signs when unusual hazards, hazardous materials, hazardous equipment, or other special conditions are present. Avoid distracting or startling persons working in the laboratory.

Use equipment only for its designated purpose Combine reagents in their appropriate order, such as adding acid to water. Avoid adding solids to hot liquids. All laboratory personnel should place emphasis on safety and chemical hygiene at all times. Never leave containers of chemicals open. All containers must have appropriate labels. Unlabeled chemicals should never be used. Do not taste or intentionally sniff chemicals. Never consume and/or store food or beverages or apply cosmetics in areas where hazardous chemicals are used or stored. Do not use mouth suction for pipe ting or starting a siphon. Access to laboratories and support areas such as stockrooms or specialized laboratories should be limited to approved personnel only. All equipment should be regularly inspected for wear or deterioration. Equipment should be maintained according to the manufacturer's requirements and records of certification, maintenance, or repairs should be maintained for the life of the equipment. Designated and well-marked waste storage locations are necessary. No cell phone or ear bud usage is allowed in the active portion of the laboratories or during experimental operations. Clothing made of synthetic fibres should not be worn while working with flammable liquids or when a hazard is present as these materials tend to melt and stick to exposed skin. Laboratory coats should not be stored in offices or break rooms as this spreads contaminates to other areas. Computers and instrumentation should be labelled to indicate whether gloves should be worn or not. Inconsistent glove use around keyboards is a source of potential contamination. Avoid wearing jewellery in the lab as this can post multiple safety hazards.

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1.2. Introduction Hazardous Chemicals and MSDS:

Material Safety Data Sheet (MSDS) provides basic information on a material or chemical product. A MSDS describes the properties and potential hazards of the material, how to use it safely, and what to do in an emergency.A material safety data sheet (or MSDS) is a document that provides workers with procedures for safely handling or working with a particular substance. Its main purpose is to aid occupational health by informing workers about the dangers of the substances they use and how to reduce their risk, both daily and in emergency situations. It includes technical information about the substance, instructions about protective equipment, and how to handle spills, dangerous exposures, storage, disposal, and fires. Some of these latter parts are helpful to emergency services, including doctors, nurses, and fire-fighters. It is therefore often required that MSDS documents are available to emergency services. When looking at an MSDS as a worker, there are three important things to focus on. These include health hazards, which deal with first aid measures and what happens when someone accidentally swallows a chemical or gets it on their skin; fire hazards, including what is required to put out a fire caused by the burning of the material; and reactivity hazards, which are about what happens when two chemicals are mixed together.

1.3 Introduction Handling Of Chemicals and Safety Requirements:

Always treat any liquid in chemical area as acid because few acids like HF may look and feel like water. All spills and leakage should be cleaned up immediately. Safety equipments such as fire extinguishers, Eye wash basin and safety showers shall be kept clean and readily accessible. Protective Equipment Educate your employees on selecting the correct PPE (personal protective equipment) to use when handling different chemicals. Required PPE may include gloves, footwear, facemasks and goggles. Safety equipment also needs to be comfortable to prevent incidents from occurring. For example, if touch sensitivity is essential for a task, textured and thin gloves are required to ensure agile movement. Handling Practiceseach chemical used within your organisation should have a specific procedure for safe handling. Ensure all employees are familiar with this. Essential aspects of safe handling practices are: Reading & re-reading each chemical SDS to minimize the risk of mishandling. Wearing PPE Dispensing of hazardous chemicals appropriately. Being prepared for emergencies with first aid. Not working with or handling chemicals while alone. Using all precautions to avoid spillage, leakage or dropping chemicals during transportation. Use specialised carriers and carts, such as a transportable gas bottle trolley the start of 2017 GHS labelling for primary and secondary containers became mandatory in most Australian states. The GHS provides a universal standard for the labelling of hazardous goods, and includes information on chemical hazards, as well as storage instructions, placards, and Safety Data Sheets Manufacturers and suppliers should always have the correct GHS labelling on hazardous goods, so it’s important to ensure everyone understands how to read GHS labels, and is familiar with the requirements for labelling Some chemicals can pose serious health hazards if they come into contact with, or are stored with, one another

II. LABORATORY TECHNIQUE

The laboratory apparatus for carrying out reactions, in general, is made up of glass. It is because glass is resistant to the action of most of the chemicals. Generally, two types of glass are used for making apparatus for laboratory work. These are soda-lime glass and borosilicate glass.Soda-lime glass, which is made by heating soda, limestone and silica, softens readily at about 300-400°C in the burner flame. Therefore, on heating glass tub made of soda-lime glass easily softens and can be bent. Coefficient of expansion of soda glass is very high, therefore on sudden heating and cooling, itmay break. To avoid breaking, it should be heated and cooled gradually. Annealing by mild reheating and uniform cooling prevents breakage. Such glass should not be kept on cold surface while it is hot, since sudden cooling may break it. Borosilicate glass does not soften below 700-800°C and requires oxygen natural gas flame for working. Natural gas mixed with oxygen is burnt to get the oxygen-natural gas flame. Coefficient of expansion of this glass is low and apparatus made of this glass can withstand sudden changes in temperature. Therefore, apparatus used for heating purposes is made from borosilicate glass. On heating, glass apparatus made up of borosilicate glass does not distort.

2.1 General Techniques

Basic laboratory skills are the techniques required for conducting experiments. These include pouring, measuring, filtration, and using gas burners and glassware. The laboratory apparatus for carrying out reactions, in general, is made

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2.2. Chromatography:

Chromatography is an important biophysical technique that enables the separation, identification, and purification of the components of a mixture for qualitative and quantitative analysis. Proteins can be purified based on characteristics such as size and shape, total charge, hydrophobic groups present on the surface, and binding capacity with the stationary phase. Four separation techniques based on molecular characteristics and interaction type use mechanisms of ion exchange, surface adsorption, partition, and size exclusion. Other chromatography techniques are based on the stationary bed, including column, thin layer, and paper chromatography. Column chromatography is one of the most common methods of protein purification.Chromatography is based on the principle where molecules in mixture applied onto the surface or into the solid, and fluid stationary phase (stable phase) is separating from each other while moving with the aid of a mobile phase. The factors effective on this separation process include molecular characteristics related to adsorption (liquid-solid), partition (liquid-solid), and affinity or differences among their molecular weights. Because of these differences, some components of the mixture stay longer in the stationary phase, and they move slowly in the chromatography system, while others pass rapidly into mobilephase, and leave the system faster. Based on this approach three components form the basis of the chromatography technique.Stationary phase: This phase is always composed of a “solid” phase or “a layer of a liquid adsorbed on the surface a solid support”.Mobile phase: This phase is always composed of “liquid” or a “gaseous component. Separated molecules. The type of interaction between stationary phase, mobile phase, and substances contained in the mixture is the basic component effective on separation of molecules from each other. Chromatography methods based on partition are very effective on separation, and identification of small molecules as amino acids, carbohydrates, and fatty acids. However, affinity chromatographies (i.e. ion-exchange chromatography) are more effective in the separation of macromolecules as nucleic acids, and proteins. Paper chromatography is used in the separation of proteins, and in studies related to protein synthesis; gas-liquid chromatography is utilized in the separation of alcohol, ester, lipid, and amino groups, and observation of enzymatic interactions, while molecular-sieve chromatography is employed especially for the determination of molecular weights of proteins. Agar’s-gel chromatography is used for the purification of RNA, DNA particles, and viruses. Various chromatography methods have been developed to that end. Some of them include.

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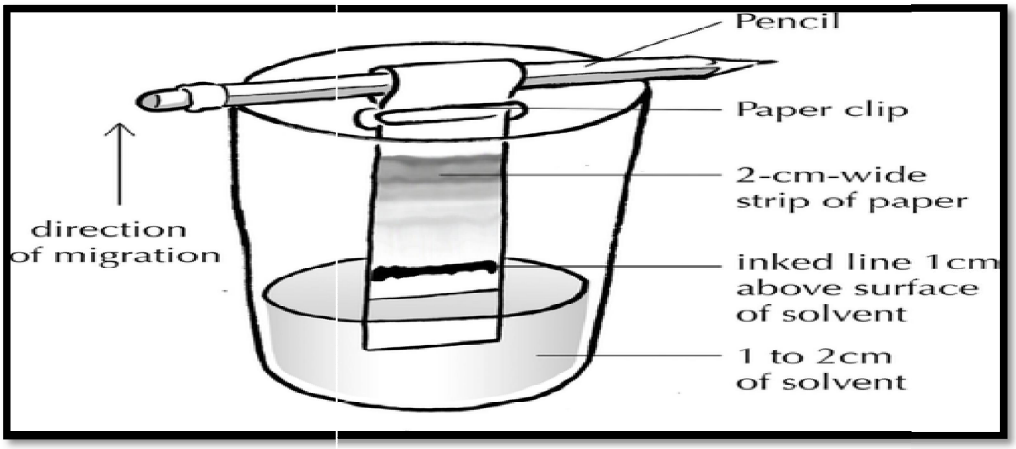

Figure: 2.2. Chromatography

2.2.1 Thin-layer chromatography (TLC):

The separation of compounds is due to the differences in their attraction to the stationary phase and because of differences in solubility in the solvent. As a result, the compounds and the mobile phase compete for binding sites on the stationary phase. Different compounds in the sample mixture travel at different rates due to the differences in their partition coefficients.Different solvents, or different solvent mixtures, give different separation. The retardation factor (RF), or retention factor, quantifies the results. It is the distance travelled by a given substance divided by the distance travelled by the mobile phase

2.2.2 Paper chromatography:

The method consists of applying the test solution or sample as a spot near one corner of a sheet of filter paper. The paper is initially impregnated with some suitable solvent to create a stationary liquid phase. An edge of the paper close to the test spot is then immersed in another solvent in which the components of the mixture are soluble in varying degrees. The solvent penetrates the paper by capillary action and, in passing over the sample spot, carries along with it the various components of the sample. The components move with the flowing solvent at velocities that are dependent on their solubility in the stationary and flowing solvents. Separation of the components is brought about if there are differences in their relative solubility's in the two solvents. Before the flowing solvent reaches the farther edge of the paper, both solvents are evaporated, and the location of the separated components is identified, usually by application of reagents that form coloured compounds with the separated substances. The separated components appear as individual spots on the path of the solvent. If the solvent flowing in one direction is not able to separate all the components satisfactorily, the paper may be turned 90° and the process repeated using another solvent.

2.2.3 Gas chromatography:

Gas chromatography (GC), along with other chromatographic techniques, is vitally important in forensic science to separate substances of analytical interest. GC is the primary technique for the analysis of fire residues. In the vast majority of cases, petroleum products are used as accelerants in fires and the peak patterns from the GC analysis can be used to identify the type of product (e.g., gasoline).

2.2.4 Ion exchange chromatography:

Ion exchange chromatography (or ion chromatography) is a process that allows the separation of ions and polar molecules based on their affinity to ion exchangers.The principle of separation is thus by reversible exchange of ions between the target ions present in the sample solution to the ions present on ion exchangers.In this process, two types of exchangers i.e., cationic and anionic exchangers can be used.

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2.2.5 Gel permeation chromatography:

Gel permeation chromatography (size-exclusion chromatography) can be used on holmic acids or folic acids in water and is frequently applied to the analysis of fatty samples such as fish. Gel permeation chromatography is a very effective method based on differences in molecular mass. Large molecules are excluded from the pores of the gels and are eluted first. This technique can easily be automated. However, after gel permeation chromatography for fractionation, additional liquid–solid column chromatography is still necessary. Thus, there is little advantage in using gel permeation chromatography for the cleanup of less fatty or no fatty samples such as water

2.2.6 High-pressure liquid chromatography:

The purification takes place in a separation column between a stationary and a mobile phase.The stationary phase is a granular material with very small porous particles in a separation column.The mobile phase, on the other hand, is a solvent or solvent mixture which is forced at high pressure through the separation column.Via a valve with a connected sample loop, i.e. a small tube or a capillary made of stainless steel, the sample is injected into the mobile phase flow from the pump to the separation column using a syringe.Subsequently, the individual components of the sample migrate through the column at different rates because they are retained to a varying degree by interactions with the stationary phase.After leaving the column, the individual substances are detected by a suitable detector and passed on as a signal to the HPLC software on the computer.At the end of this operation/run, a chromatogram in the HPLC software on the computer is obtained.The chromatogram allows the identification and quantification of the different substances.

2.2.7 Affinity chromatography:

Affinity chromatography is one of the most diverse and powerful chromatographic methods for purification of a specific molecule or a group of molecules from complex mixtures. It is based on highly specific biological interactions between two molecules, such as interactions between enzyme and substrate, receptor and legand, or antibody and antigen. These interactions, which are typically reversible, are used for purification by placing one of the interacting molecules, referred to as affinity ligand, onto a solid matrix to create a stationary phase while the target molecule is in the mobile phase. Successful affinity purification requires a certain degree of knowledge and understanding of the nature of interactions between the target molecule and the ligand to help determine the selection of an appropriate affinity ligand and purification procedure. With the growing popularity of affinity purification, many of the commonly used ligands coupled to affinity matrices are now commercially available and are ready to use. However, in some cases new affinity chromatographic material may need to be developed by coupling the ligand onto the matrix such that the ligand retains specific binding affinity for the molecule of interest. In this chapter, we discuss factors which are important to consider when selecting the ligand, proper attachment chemistry, and the matrix. In recent years, matrices with unique features which overcome some of the limitations of moretraditional materials have been developed and these are also described. Affinity purification can provide significant time savings and several hundred-fold or higher purification, but the success depends on the method used. Thus, it is important to optimize the purification protocol to achieve efficient capture and maximum recovery of the target.

2.3.Crystallization:

Crystallization is the process of atoms or molecules arranging into a well-defined, rigid crystal lattice in order to minimize their energetic state. The smallest entity of a crystal lattice is called a unit cell, which can accept atoms or molecules to grow a macroscopic crystal.During crystallization, atoms and unit cells bind together with well-defined angles to form a characteristic crystal shape with smooth surfaces and facets. Crystallization can occur in nature but also has broad industrial applications as a separation and purification step in the pharmaceutical, chemical, and food industries. Crystallization touches every aspect of our lives from the foods we eat and the medicines we take to the fuels we use to power our communities. The majority of agrochemical and pharmaceutical products go through many crystallization steps during their development and manufacture.In the food industry, ingredients such as lactose and lysine are delivered as crystals to humans and animals for consumption. A major safety concern for the petrochemical industry is the unwanted crystallization of gas hydrates in deep sea pipelines.This is why scientists and engineers in multiple industries around the world are required to understand, optimize and control crystallization processes every

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day. Effective and efficient crystallization ensures high quality and safe production.Crystallization is important in product quality because it influences particle size, purity and product yield. For example, in the pharmaceutical industry, the crystallization of an active pharmaceutical ingredient (API) needs to be strictly controlled to meet desired product specifications.Traditional crystallization techniques include hanging-drop or sitting-drop vapor diffusion, and the micro-batch method. Vapour diffusion and micro-batch crystallization techniques are commonly used for proteins.

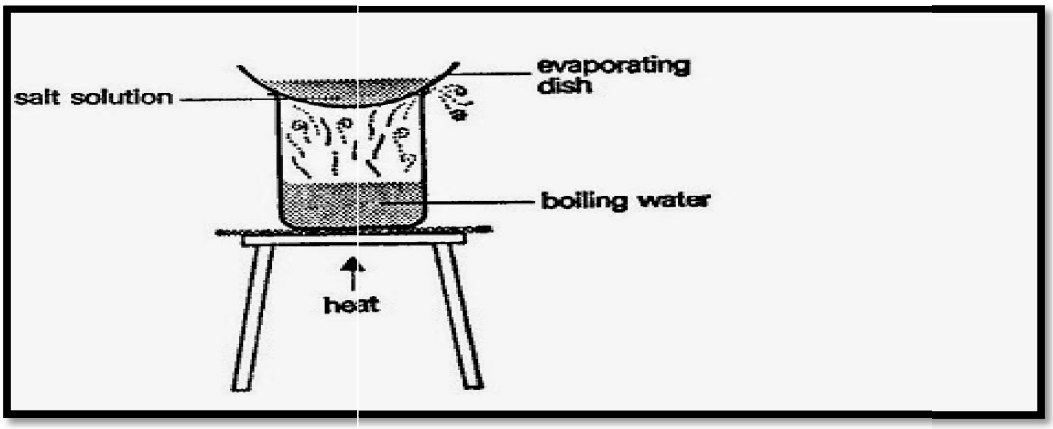

Figure:2.3. Crystallization

2.4 Extraction :

Extraction is the first step to separate the desired natural products from the raw materials. Extraction methods include solvent extraction, distillation method, pressing and sublimation according to the extraction principle. Solvent extraction is the most widely used method. The extraction of natural products progresses through the following stages: the solvent penetrates into the solid matrix; the solute dissolves in the solvents the solute is diffused out of the solid matrix; the extracted solutes are collected. Any factor enhancing the diffusivity and solubility in the above steps will facilitate the extraction. The properties of the extraction solvent, the particle size of the raw materials, the solvent-to-solid ration, the extraction temperature and the extraction duration will affect the extraction efficiency. The selection of the solvent is crucial for solvent extraction. Selectivity, solubility, cost and safety should be considered in selection of solvents. Based on the law of similarity and inter miscibility (like dissolves like), solvents with a polarity value near to the polarity of the solute are likely to perform better and vice versa. Alcohols (EtOH and MeOH) are universal solvents in solvent extraction for physicals tochemicals investigation.Generally, the finer the particle size is, the better result the extraction achieves. The extraction efficiency will be enhanced by the small particle size due to the enhanced penetration of solvents and diffusion of solutes. Too fine particle size, however, will cost the excessive absorption of solute in solid and difficulty in subsequent filtration.High temperatures increase the solubility and diffusion. Temperatures that too high, however, may cause solvents to be lost, leading to extracts of undesirable impurities and the decomposition of thecomponents.The extraction efficiency increases with the increase in extraction duration in a certain time range. Increasing time will not affect the extraction after the equilibrium of the solute is reached inside and outside the solid material.The greater the solvent-to-solid ratio is, the higher the extraction yield is; however, a solvent-to-solid ratio that is too high will cause excessive extraction solvent and requires a long time for concentration. The conventional extraction methods, including maceration, percolation and reflux extraction, usually use organic solvents and require a large volume of solvents and long extraction time. Some modern or greener extraction methods such as super critical fluid extraction (SFC), pressurized liquid extraction (PLE) and microwave assisted extraction (MAE), have also been applied in natural products extraction, and they offer some advantages such as lower organic solvent consumption, shorter extraction time and higher selectivity. Some extraction methods, however, such as sublimation, expeller pressing and effleurage are rarely used in current photochemical investigation and will not discussed in this review. A brief summary of the various extraction methods used for natural products . In general, extraction procedures include maceration, digestion, decoction, infusion, percolation, Soxhlet extraction, superficial extraction, ultrasound-assisted, and microwave-assisted extractions.[32]

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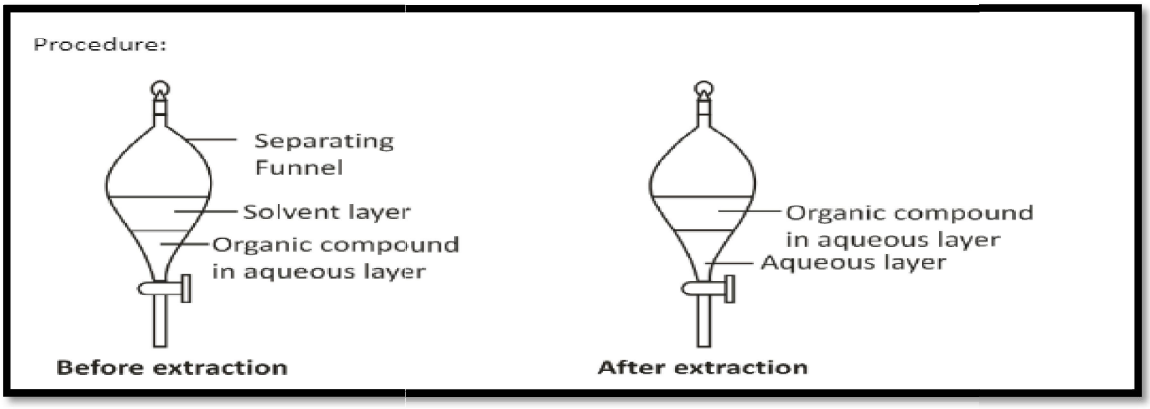

Figure:2.4 Extraction

2.5.Distillation:

Distillation is a process widely used in chemical and biochemical industries for separating and purifying components of a mixture. The technique involves heating the mixture to vaporize the volatile components, which are then condensed back into a liquid phase and collected separately. The principle of distillation is based on the difference in boiling points of the components in the mixture, which determines their ability to evaporate and condense at different temperatures. Distillation has a long history, dating back to ancient times, when it was used to extract alcohol from fermented liquids. The process was refined over time, and today, it is a critical part of many industrial processes, from the production of fuels and chemicals to the purification of pharmaceuticals and food products. In this article, we will discuss the distillation process in detail and explore its importance in modern industrial applications.The basic setup of a distillation apparatus consists of a vessel called a still, which contains the mixture to be distilled, and a condenser, which cools the vapour and condenses it back into a liquid. The still is heated to vaporize the volatile components of the mixture, which rise and pass through a column packed with materials that enhance the separation process. The column is designed to provide a large surface area for the vapour to come into contact with, and it may contain trays or packing material to increase the separation efficiency.As the vapour rises through the column, it cools and condenses on the surface of the packing material. The condensed liquid then flows back down the column and collects in a separate vessel. The process continues until all the volatile components have been separated and collected. The temperature of the still is carefully controlled to ensure that only the desired components are vaporized and condensed, while the non-volatile components remain in the still.The importance of distillation -Distillation is a critical technique in many industrial processes, as it allows for the separation and purification of components from complex mixtures. For example, in the petroleum industry, crude oil is distilled to separate it into its various components, such as gasoline, diesel, and lubricating oils. Similarly, in the production of chemicals, distillation is used purify the final product and remove impurities and by-products. Distillation is the process during which a liquid is heated to boiling point in order to vaporize it, and then condensed back into liquid so that it is separated from impurities or other solutes.

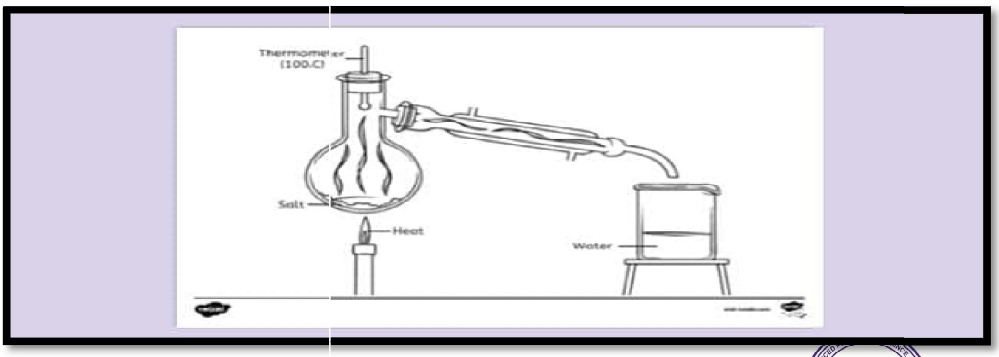

Figure:2.5 Distillations

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2.5.1 Overview of Distillation :

Distillation is used to separate liquids from non-volatile solids, as in the separation of alcoholic liquors from fermented materials, or in the separation of two or more liquids having different boiling points, as in the separation of gasoline, kerosene, and lubricating oil from crude oil.

2.5.2 Simple Distillation:

Simple distillation works to effectively separate liquids due to the unique properties of liquids. In particular, all liquids involve equilibrium between the condensed liquid phase and a layer of vapour above the liquid. As temperature increases, more liquid molecules have enough energy to liberate from the liquid as vapour. This increases the pressure exerted by the vapour on the liquid, called vapour pressure. When the liquid heats so much that it reaches beyond its boiling point, all the liquid converts to vapour at equilibrium. Thus, at a given temperature, liquids with lower boiling points have higher vapour pressures than those with higher boiling points, as more volatile liquids are closer to becoming completely gas.When two liquids form a homogenous mixture, any increase in temperature will release vapours from both liquids. However as mentioned before, the more volatile component releases more vapour than other. The exact proportion of a component in the vapour mixture depends on its vapour pressure and its mole fraction in the liquid mixture. A method of separating mixtures based on differences in their volatilities in a boiling liquid mixture. The components in a sample mixture are vaporised by the application of heat and then immediately cooled by the action of cold water in a condenser.

2.5.3 Fractional Distillation:

Fractional distillation is used when separating mixtures of liquids whose boiling points are similar (separated by less than 70 C). In a fractional distillation, a mixture of liquids is boiled and the resulting vapours travel up a glass tube called a “fractionating column” and separate. The fractionating column is placed between the flask containing the mixture and the “Y” adaptor and improves the separation between the liquids being distilled. Fractional distillation leads to a better separation than simple distillation because the glass beads in the fractionating column provide "theoretical plates" on which the vapours can condense and then re-evaporate, and re-condense, essentially distilling the compound many times over. One theoretical plate is equivalent to one vaporization-condensation cycle, which is equivalent to one simple distillation. The more volatile liquids will gradually move towards the top of the fractionating column, while higher boiling liquids will stay towards the bottom, giving a better separation between the liquids. The vapour eventually reaches the condenser, where it is cooled and then drips in to the collection vessel. The column used the optimal length is a function of the proximity of the boiling point of the desired material to the impurity. Keep in mind, the longer the Vigreux, the lower the recovery.

2.5.4 Vacuum Distillation:

A distillation operation that is performed at a pressure below atmospheric pressure is called vacuum distillation. In other words, distillation under reduced pressure is known as Vacuum distillation. This is performed by lowering the pressures in the column or the reactorVacuum distillation working principle .When you have a solution that you need to separate using distillation, you need to heat the mixture above the boiling point of one component so that it can be converted into vapour form and then condensed to cover again in liquid form.If the boiling point of the component is very high (generally boiling point of more than 150 is considered high) it is difficult to achieve as it requires a utility that can evaporate it which can be costly. So the pressure of the column is reduced, as pressure decrease, the boiling point of the compound also decrease. This decrease in the boiling point of the compound can be achieved with cost-effective utilities also and can achieve easily

2.5.5 Steam Distillation:

Steam distillation is a separation process which purifies isolate temperature-sensitive materials, such as natural aromatic compounds. In steam distillation, dry steam is passed through the plant material. These vapours undergo condensation and collection in receivers.We use steam distillation for extraction of essential oil. Steam distillation implements low-

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pressure steam, this replaces the volatile compounds from the intact plant material. Furthermore, steam distillation allows us to control the temperature and amount of steam that we apply to the plant materials.

2.5.6 Rotary Evaporation:

Rotary evaporation is the process of reducing the volume of a solvent by distributing it as a thin film across the interior of a vessel at elevated temperature and reduced pressure. This promotes the rapid removal of excess solvent from less volatile sample.

2.6 Other Techniques:

2.6.1 Determination of Melting Point:

The point at which changes solid form convert to liquid form.Temperature at which the solid and liquid forms of a pure substance can exist in equilibrium. As heat is applied to a solid, its temperature will increase until the melting point is reached. More heat then will convert the solid into a liquid with no temperature change. When the entire solid has melted, additional heat will raise the temperature of the liquid. The melting temperature of crystalline solids is a characteristic figure and is used to identify pure compounds and elements. Most mixtures and amorphous solids melt over a range of temperatures

2.6.2 Determination of BoilingPoint:

The point at which liquid is convert to the vapour form .Boiling point, temperature at which the pressure exerted by the surroundings upon a liquid is equal by the pressure exerted by the vapour of the liquid; under this condition, addition of heat results in the transformation of the liquid into its vapour without raising the temperature .[

2.6.3 Determination of Sublimation:

The point solid is converting to gaseous form without its becoming liquidSublimation, in physics, conversion of a substance from the solid to the gaseous state without its becoming liquid. An example is the vaporization of frozen carbon dioxide (dry ice) at ordinary atmospheric pressure and temperature. The phenomenon is the result of vapour pressure and temperature relationships. Freeze-drying of food to preserve it involves sublimation of water from the food in a frozen state under high vacuum. See also vaporization; phase diagram.

2.6.4 Determination of Chemical Tests:

It is identify or characterised organic compound.Chemical testing or chemical analysis is vital for regulatory compliance and to understand the quality and composition of chemical substances and materials that are used in products, industrial processes and manufacturing. Specialist industry knowledge and expertise in applying the most relevant methodology are the keys to successful chemical testing. Advanced analytical instrumentation or a combination of techniques is necessary to solve problems or determine composition.We provide advanced research and testing expertise, and operate under ISO 17025, Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and other recognized industry standards. We perform testing protocols according to standard methodologies (ISO, EN, BS, ASTM, DIN, etc.) and are experts in developing tailored analytical methods and performing method validation for specific testing applications.Example Oxidation reaction,Hydrolysis reaction

2.7 Reaction Workups:

A key step in this sequence comes immediately after the reaction is complete, and is called the reaction "work-up" .The work-up refers to methods aimed at purifying the material, and most commonly occurin separating funnel. Solutions are added to the funnel to either extract or wash the mixture, with the goal of isolating the product from excess reagents, catalysts, side products, solvents, or compounds formed from side reactions. When the goal of an experiment is to conduct a reaction and isolate the product, the general sequence of events are follows a) conduct the reaction.b) Perform multiple extractions and/or washes to partially purify the desiredproduct.c) Remove traces water with a drying agent.d) Filter or decant the drying agent.e) Remove the solvent with a rotary evaporatorf) further purify if necessary

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, January 2024

III. API TECHNOLOGY

Active pharmaceutical ingredients (APIs) are the chemical-based compounds that have produced mainly in the countries the USA, Europe, China, and India. APIs have pharmacological activity mainly used with combination of other ingredients to diagnose, cure, mitigate, and treat the disease. However, in the recent past years, many medicinal-based corporations have started importing these substances from countries producing active ingredients to their home countries. Modern day medicines have been used by people to prevent, treat, diagnose, and cure disease. Every single medication is composed of two main components, i.e. the API, which is the major component, is chemically and biologically active that has to do the work in your body and other component known as excipient like lactose or mineral oil in the pill, which is chemically inactive that provides, e.g. volume, a sweet flavour, or a colour. These excipients helps in the delivery of APIs in the body system. Numerous chemical compounds and raw materials are utilized in multi-step reaction to make an API. However, their main purpose is to treat the disease directly by acting upon (via their pharmacological activity) along with combination of inactive form. Nearly more than 1 lakh tones of pharmaceutical products are consumed all over the globe (e.g. Europe alone covers up to 24% of the consumption of medicinal products). Therefore, the generation of these APIs has stimulated the release of chemicals in the environment and thereby lead to the spreading of pollution. Concurrently, this enormous generation of pollution has called the worldwide attention that requires an immediate alteration in the policies and regulation.

3.1 Overview ofAPI:

Active ingredients are the substances in drugs that are responsible for the beneficial health effects experienced by consumers. The active ingredient in a pharmaceutical drug is called an active pharmaceutical ingredient (API). An example of an API is the acetaminophen contained in a pain relief tablet. Active pharmaceutical ingredients (APIs) are the active components in a pharmaceutical drug that produce the required effect on the body to treat a condition. APIs are produced by processing chemical compounds. In a biologic drug, the active ingredient is known as a bulk process intermediate.[1]

3.1.1 API Intermediate and Fine Chemical Industry:

There are some biochemical constituents known as Active Pharmaceutical Ingredients intermediates that are engaged in the manufacturing of APIs. Though they are not APIs they contribute to the manufacturing of the end products and their quality matters a lot. Active Pharmaceutical Ingredients are the elements or things that are used as the building blocks for producing active pharmacological components. Contract API Manufacturing has created a sound base for the production of API intermediates.

INDUSRIES

Tata Chemicals Ltd., UPLLtd., PI Industries Ltd. , Aarti Industries Ltd. , Deepak Nitrite Ltd.,Gujarat Fluoro-chemicals Ltd.

3.2 Unit Process in Synthesis:

Pharmaceutical Processing is the process of drug manufacturing and can be broken down into a range of unit operations, such as blending, granulation, milling, coating, tablet pressing, filling, and others. The Pharmaceutical manufacturing process has precise requirements and manufacturing guidelines for quality.

3.3 Optimization of Organic Reactions and Processes:

Chemical reaction optimization is a term that has a variety of meanings depending on the chemist defining it, with a large corresponding variance in expectations of optimization capability and proficiency. As reaction optimization is largely unexplored during undergraduate chemistry teaching, (1−3) many research chemists are simply unaware of existing optimization techniques and are therefore unlikely to employ robust strategies in their workflows as their career progresses. This is particularly true in academic research, where intuition-based optimization is commonplace despite the increasing evidence showing that reaction algorithmic optimizations are more efficient in relation to both time and material and therefore cost For these reasons, the use of these methodologies is much more widespread in industrial research and development, particularly in process laboratories compared to their discovery laboratory counterparts, as

IJARSCT
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International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, January 2024

manufacturing conditions often result from vigorous optimization protocols. Consequently, there is often a large disparity in the familiarity of optimization techniques between industrial and academic researchers, particularly because industrial scientists also often have internal multidisciplinary teams of statisticians and process chemists to collaborate with. However, the techniques covered are not inaccessible for chemists, and increasing the exposure of these methodologies will make them more widespread across both academic research and teaching, thereby enriching the skill set of the entire chemical community. Although the primary aims of many scientists (particularly synthetic chemists) may not be to achieve truly optimal processes, familiarity with the concepts discussed herein will help researchers meet the needs of the modern and evolving laboratory.This review aims to critically analyze and compare major chemical reaction optimization techniques, thereby helping to deliver an accessible account of optimization strategies (with references to their applications) for the general chemical scientist. As many of these methodologies borrow concepts from related fields, such as statistics, computer science, process chemistry, and engineering, this review will help to diversify the chemist's toolkit and serve as a comprehensible reference for optimization campaigns. Although reaction optimization is often related to reaction yields, it may also be performed with respect to purity, E-factor, enantiomeric excess, etc., and these concepts will be explored further. Typical reaction variables that are optimized are also often described as either continuous (in a numeric form, such as temperature or reaction time) or categorical (discrete options, such as solvent or catalyst/ligand choice). Further in-depth reading will also be provided at each stage for interested scientists seeking a deeper understanding of the workings of each methodology. We also discuss how to explore the generated reaction knowledge within the subsequent process scale-up efforts. By providing tools for considerations of scale-up challenges and complexity in the early stages of process optimization, we hope to help chemists to guide their optimization efforts toward scalable processes and thus facilitate the translation of critical laboratory discoveries into commercially available products.

3.4 Industrial Process and Scale-up Techniques:

Industrial manufacturing methods and flow charts of APIs

Process methods are key components of quality control in a chemical manufacturing plant. These methods ensure that a production reaction step conducted by trained operators within the entire validated process will produce a quality chemical entity in the expected yields.

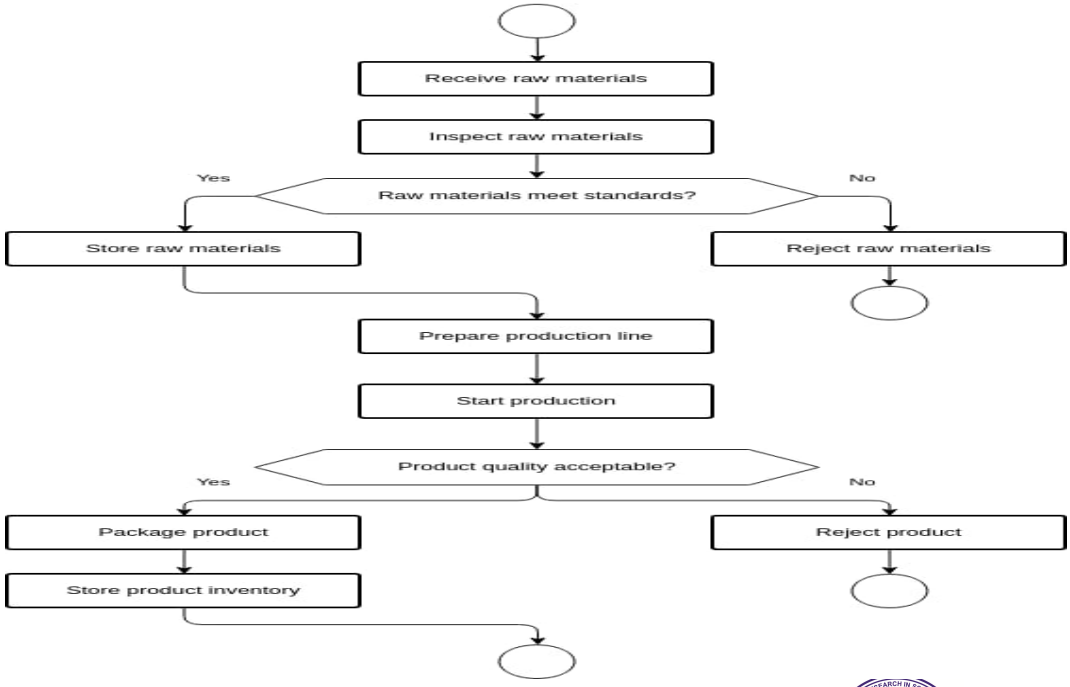

Figure: 3.4 Chirality

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ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
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Impact Factor: 7.53
Volume 4, Issue 2, January 2024

The presence of impurities and related compounds (derived from the reaction or secondary reactions) is a critical parameter that determines a synthetic material's quality.Chemical processing differs from product manufacturing. For example, the manufacture of a finished product typically involves a molecular entity that is stable under normal conditions and can be stored for prolonged periods without losing its physical and chemical characteristics. Most chemical reactions, however, require very tight controls and close monitoring of their progress because any of several potential result paths may be followed if conditions are not monitored closely. Other factors such as temperature and pressure are critical parameters for the successful completion of the chemical conversion processing Process Control Methods for the Manufacture of APIs.

3.5 Chirality in the API Industry:

3.5.1. Chirality:

Chirality in molecular structure introduces substantial complexity in characterizing drug behaviour with PK-PD models if the chiral drug is studied as a racemate.58 Taken from the Greek word chier (meaning hand), “chiral” is the term used to designate a molecule that has a centre (or centre) of three-dimensional asymmetry. Most of the organic chiral molecules in the pharmaceutical industry contain an asymmetric carbon centre, meaning they have a unique three-dimensional shape and are not completely identical to their mirror image.Example lactic acid

3.5.2 Resolution Race-mate:

Separation of race mates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of race mates. Reaction of a race mate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, whichcan be separated. Reversing the first reaction then leads to the separated enantiomers plus the recovered reagent.Many kinds of chemical and physical reactions, including salt formation, may be used to achieve the diastereomeric intermediates needed for separation. The following diagram illustrates this general principle by showing how a nut having a right-handed thread (R) could serve as a "reagent" to discriminate and separate a mixture of right- and left-handed bolts of identical size and weight. Only the two right-handed partners can interact to give a fully-threadedintermediate, so separation is fairly simple. The resolving moiety, i.e. the nut, is then removed, leaving the bolts separated into their right and left-handed forms. Chemical reactions of enantiomers are normally not so dramatically different, but a practical distinction is nevertheless possiblechiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of race mates into their component enantiomers is a process called resolution.

3.5.3 Asymmetric Synthesis

Asymmetric synthesis is a subclass of stereo-selective reactions, where a new chiral stereogenic unit is created during a reaction. The new stereogenic unit can be a chiral centre, a chiral axis or a chiral plane. The reaction must proceed with unequalformation of possible stereo-isomers. The chiral unit can be produced from substrates bearing pro-chiral units such as pro-chiral centre, a pro-chiral plane or a pro-chiral axis. The pro-chiral unit can be enantiomer topic or distereotopic. Thus, two essential components of asymmetric synthesis are:Conversion of a pro-chiral unit to a chiral unit; andFormation of unequal proportions of possible chiral stereo-isomers.

3.6. Polymorphism in APIs

Different polymorphs of the same active pharmaceutical ingredient (API) display distinct physical properties, such as melting point, solubility, dissolution rate, hygroscopicity, or stability. The ability to successfully produce and reproduce specific stable polymorphs is intricately correlated with the efficiency and speed of drug development, the robustness of manufacturing process, and – ultimately – the stability and quality of APIs. This paper focuses on eight case study examples of interesting polymorphic transformations observed in the course of the regular API development process. Through extensive physicochemical characterization, using multiple analytical techniques, the phenomena observed could be elucidated and proper measures recommended to reduce the risk of unexpected.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
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Impact Factor: 7.53
Volume 4, Issue 2, January 2024

3.7 .APIs:Overview of QA, QC, and GMP guidelines in API manufacturing (ICH Q7, Q7A, and Q11):

3.7.1. QUALITY ASSURANCE:

Quality assurance (QA) is any systematic process of determining whether a product or service meets specified requirements.QA establishes and maintains set requirements for developing or manufacturing reliable products. A quality assurance system is meant to increase customer confidence and a company's credibility, while also improving work processes and efficiency, and it enables a company to better compete with others.The ISO (International Organization for Standardization) is a driving force behind QA practices and mapping the processes used to implement QA. QA is often paired with the ISO 9000 international standard. Many companies use ISO 9000 to ensure that their quality assurance system is in place and effective.The concept of QA as a formalized practice started in the manufacturing industry, and it has since spread to most industries, including software development.Quality assurance utilizes one of three methods:Failure testing, which continually tests a product to determine if it breaks orfails. For physical products that need to withstand stress, this could involve testing the product under heat, pressure or vibration. For software products, failure testing might involve placing the software under high usage or load conditions.

Statistical process control (SPC)

A methodology based on objective data and analysis and developed by Walter Shewhart at Western Electric Company and Bell Telephone Laboratories in the 1920's and 1930's. This methodology uses statistical methods to manage and control the production of products.

Total quality management (TQM)

The apply quantitative methods as the basis for continuous improvement. TQM relies on facts,data and analysis to support product planning and performance review.

3.7.2 QUALITY CONTROL –

Quality does not have a singular definition. Despite the relative meaning of “value,” quality control is the process by which products/services are tested and measured to ensure they meet a standard. Through this process, a business can evaluate, maintain, and improve product quality. The primary objective of Quality Control is to identify and correct anydeviations from the established quality standards. This process involves monitoring and inspecting products or services at various stages of production or delivery to ensure that they meet the desired level of quality. QC is also concerned with preventing defects or errors from occurring in the first place by implementing measures to control and improve the production or service delivery processes

3.7.3 GMP GUIDELINES IN API MANUFACTURING:

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Q7 Good manufacturing practice for active pharmaceutical ingredients - Scientific guideline

This document provides guidance on the good manufacturing practice for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It also aims to help ensure that APIs meet the requirements for quality and purity

According to ICH Q11, a "commercially available substance" is one that is offered and sold as a commodity in the non-pharmaceutical market in addition to its use as a starting material. The term "custom synthesised" is not defined in ICH Q11; it is generally understood to be a substance which has been synthesised specifically for pharmaceutical manufacture and in consideration of a customers' requirements. The distinction between these two terms plays an important role in ICH Q11 insofar as that an applicant does not have tojustify the use of a "commercially available" substance as a starting material in the dossier - on the contrary to "custom synthesised" compounds; those are subject to the regulations of ICH Q11. The same goes for intermediates that do not count as "commercially

IJARSCT
ISSN (Online) 2581-9429
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Volume 4, Issue 2, January 2024

IV. EXPERIMENTAL TECHNIQUES

4.1 Impurity -Introduction, Classification, Source:

An impurity in a drug substance as defined by the as the drug substance in the drug product2 International Conference on Harmonisation (ICH) Guidelines1 is any component of the drug substance that is not the chemical entity defined Similarly, an impurity in a drug product is any component as the drug substance and affects the purity of active ingredient or drug substances of the drug product that is not the chemical entity. Therefore any extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties. The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and from the media. Several recent books3,4 and journal reviews5,6 address this topic and guidelines are available from US and international authorities.

CLASSIFICATION

- Organic Impurities
- Inorganic Impurities
- Residual Solvent
- SOURCES
- Raw Material
- Method of manufacturing
- Manufacturing Hazard

4.1.1 Purification and Impurity control in APIs:

In processes that use a series of chemical reaction steps to synthesise the API, the removal of reaction by-products, including colour bodies and metals, is critical to produce high quality pharmaceuticals. The preferred methods for removing residual metal catalysts are distillation, crystallisation and precipitation. A distillation collects the pure API as a distillate, leaving the non-volatile compounds in the residue, while crystallisation and precipitation steps both generate solid material that can be physically removed by selecting a filtration step. In addition, both chromatography and activated carbon powder treatments are used.

4.2 Biological as API:

Biological API Drug or Active Pharmaceutical Ingredient is the part of a drug that contains the medicine for intended effects. Some drugs contain multiple active ingredients that are used for treating different symptoms in different ways. The name of the active ingredient is contained on the package of the medicine. The biological API drug manufacturing is done to furnish the direct effects of the medicine in the cure, treatment, mitigation, prevention and cure of any disease. The manufacturing process undergoes a chemical test where the API drug is tested for the needed effect.The Biological API Drug Manufacturing is done from raw materials using many chemical compounds. The chemical compound that goes through the process of becoming an API from a raw material is called an intermediate. During this manufacturing process, it is purified until it reaches a very high degree of purity and finally processes into an API.

4.3 Regulations as Biological:

Biological regulation is what allows an organism to handle the effects of a perturbation, modulating its own constitutive dynamics in response to particular changes in internal and 8 Feb 2022external conditions. With the central focus of analysis on the case of minimal living systems, we argue that regulation consists in a specific form of second-order control, exerted over the core (constitutive) regime of production and maintenance of the components that actually put together the organism. The main argument is that regulation requires a distinctive architecture of functional relationships, and specifically the action of a dedicated subsystem whose activity is dynamically decoupled from that of the constitutive regime. We distinguish between two major ways in which control mechanisms contribute to the maintenance of a biological organisation in response to internal and external perturbations: dynamic stability and regulation. Based on this distinction an explicit definition and a set of organisational requirements for regulation are

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
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Impact Factor: 7.53
Volume 4, Issue 2, January 2024

provided, and thoroughly illustrated through the examples of bacterial chemo taxis and the lac-operon. The analysis enables us to mark, out the differences between regulation and closely related concept.

4.4 Packaging and Repackaging of APIs

The final step in packaging and labelling an active pharmaceutical ingredient (API) can also be considered as the first step in the manufacture of a dosage form. Consequently this step is important and should be performed in a manner consistent with the dosage form GMP requirements.

V. STANDARD REQUIREMENTS

A. Areas used for packaging of active pharmaceutical ingredients (API) where the API will not undergo further purification steps, need to meet the standards of the current GMP for cleanliness. The facilities and controls used should be nominally equal to those for the formulation of non-sterile drug products.

B. The generation and handling of labels for API must conform to customer and local requirements.

C. Appropriate procedures shall be in place to make sure the area used for the packaging and labelling operation has been cleared of other APIs, labelling, and packaging components from previous operations immediately prior to use.

D. The area, scales, equipment, utensils, etc., shall be cleaned if a different API was previously handled prior to processing the next scheduled batch such that cross contamination does not occur.

E. The clearance of the area will be described in unit procedures and documented in appropriate log(s) or records.

F. Systems shall be in place to assure the correct API is packaged, the correct labels applied, and appropriate packaging materials used.

G. Only containers and closures approved by QA/QC may be used. Approved in the above context means the packaging components are evaluated in the API stability testing program, conform to regulatory requirements and each batch of a container or closure which is in direct contact with the API is released by QA/QC.

H. Each container packaged must have a label or a suitable means of insuring the identity (API name and batch number) of the material in the package. A system based on use of identification tags on each container may be used for intra- plant shipment instead of a commercial label.

I. An electronic system or a 100 percent visual examination must be performed to make sure the containers are correctly labelled.

Repackage produce cartons or vials of prescription drugs, ready to be provided to patients; others are intermediaries in delivering active pharmaceutical ingredients (APIs) to manufacturers, compounding pharmacies and others. Several businesses in the latter category have been issued warning letters by FDA for alleged violations of cGMP standards, missing documentation on certificates of quality, failure to investigate flawed packages and a variety of other complaints. Many of the warning letters focus on processes being carried out in handling based APIs.

VI. CONCLUSION

The impurity profile of pharmaceuticals is receiving increasing importance and drug and safety are receiving more and more attention from the public and from the media. This literature provides valuable information about the impurities. Nowadays, it is a mandatory requirement in various pharmacopeia to know the impurities present in API. The establishment of guidelines for impurity levels in drug substances and products provides the quality criteria for the synthesis of Drugs. The key aspect is that the impurity profiling of a new chemical entity must be shown to be qualified.

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