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A Review on Active Pharmaceutical Ingredients and Impurity Profiling

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INTRODUCTION

1) LABORATORYSAFETY

Each college that stores and uses hazardous chemicals in a laboratory setting will identify at least one Chemical Hygiene Officer (CHO) to serve as a focal point for laboratory health and safety activities within the unit and as liaison with Environmental Health and Safety. Colleges that are made up of a number of large laboratory-based departments are urged to assign laboratory safety officers within each department.

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2) HAZARDOUS CHEMICALS

Material Safety Data Sheets (MSDSs) are documents prepared by the manufactures/ suppliers of the chemicals and contain information on physical and chemical properties of the material, potential hazards of the material and how to work safely with these materials. They also contain information on usages, storage, handling and emergency procedures related to the hazards of the materials. In fact, they provide a single reference for all information about hazardous substances.

The revised (Material) Safety Data Sheets (SDS) contains Sixteen (16) Sections, however, different countries provide for 9 to 16 sections and their format varies from country to country. As per purple book on GHS, the information in the SDS should normally be presented using the following 16 headings in the order given below:

(1) Identification

(2) Hazard(s) identification

(3) Handling of Chemicals & Safety Requirement

- Always label all containers with chemicals.
- Use protective equipment's for eye protection and make sure to wear a laboratorycoat.
- Avoid intentional smelling, inhaling and tasting ofchemicals.
- Always avoid direct contact with chemicals, far from your hands face, clothes and shoes.
- Hazardous chemical should be used only as directed.
- Use separate cabinets for acid solutions with concentration more than 6 M.
- Mark the date on all containers upon receipt and again when reopened.
- Attach chemical labels with all necessary information to all containers.
- Immediately read the warning labels when opening newly received reagent chemicals. This will help to be
- aware of any special storage precautions such as refrigeration or inert atmosphere storage.
- Aperiodic check on chemical containers for rust, corrosion, and leakage is a must.
- Storebottles in chemical safe bags especially those hazardous and moisture-absorbing chemicals.

- Avoid use of mouthsuction to fill a pipette. Use a pipette bulb or other filling devices.
- Smoking, drinking, eating and the application of cosmetics is forbidden in areas where hazardous chemicals are used or stored.
- Always use chemicals with adequate ventilation. Check with the MSDS and also the Standard Operating

Procedure to workout what type of ventilation is required.

- Whenever you leave the lab after handling any chemicals wash thoroughly with soap and water. Keep your hands and face clean free from any trace of chemicals.

MODULE :-2

 LABORATORYTECHNIQUES

 CHROMATOGRAPHY

It is well known that chromatography is a laboratory technique used for separation and quantification of complex organic mixtures which cannot be separatedeffectively by other purification techniques. The constituents of a mixture dissolved in solvent get separated radiantly according to their affinities to the stationary phase with the help of mobile phase one after another. Chromatography is invented by Mikhail Semenovich Tswett in 1903

Nowadays, many different kinds of chromatography techniques, such as thin-layer chromatography (TLC), paper chromatography, and liquid chromatography (e.g., HPLC, UPLC, and preparative HPLC), supercritical fluid chromatography, and gas chromatography (GC)) have been designed and utilized for the separation and purification of pharmaceutical drugs.

In this chapter, the authors discuss the principles for chromatography method development using ultra/high- performance liquid chromatography (UPLC/HPLC) techniques for the analysis of assay and organic impurities/related substances/degradation products of pharmaceuticals (any drug product/drug substance/intermediate/raw material of pharmaceuticals).

These techniques are developed substantially as a result of the work of Archer John Porter Martin and Richard Laurence Millington Synge during the 1940s and 1950s, for which they won the 1952 Nobel Prize in Chemistry . Commonly used characterizing technique in pharma industry is liquid chromatography (e.g., HPLC, UPLC, and LC–MS). Each one varies in the stationary phase and operational conditions. HPLC and UPLC can be used as a quantitative technique if coupled with a mass detector (MS) to elucidate the structure of the molecule and quantification.

 CRYSTALLIZATION

Crystallization can be defined as the process through which the atoms/molecules of a substance arrange themselves in a well-defined three-dimensional lattice and consequently, minimize the overall energy of the system. When a substance is subjected to crystallization, its atoms or molecules bind togetherthroughwell-defined angles.

On adding a solid substance in a liquid and stirring it, the solid dissolves in the fluid. But when added more and more solid to the liquid, a point comes after which no more solid dissolves in the liquid. This point is called a saturationpoint and the fluid is called a saturation solution.

You may have seen many forms of crystals around you, but have you ever wondered what these crystals are and how they are formed? Well, here in this article we are going to discuss how these crystals are made i.e., the process of Crystallization and what are its various types. By the end of this article, you will completely understand the process of Crystallization and every term related to it. So, let's talk about crystallization.

Crystallization is a processof formation of a solid in which atoms and molecules are structuredin such a way that they are highly organized. The structure in which they are structured is called a crystal. There are many ways with the help of a crystal can be formed such as these crystals can be made by precipitating from a solution, freezing and sometimes its deposition directly from a gas. This process of crystallization depends on many factors that include temperature, pressure, time of fluid evaporation, etc. The process of crystallization can occur in two steps. In the first step, a crystalline phase appears from a supercooled liquid or a supersaturated solvent and this step is called nucleation. In the second step, we see a crystal growth i.e., the size of the particles of crystal increases and this step is called a crystal state. Crystallization can help in the separation of chemical solid liquid.

 Crystallization Process

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 Separating Substances via Crystallization

Activity:

Here is an experiment to understand crystallization clearly:

Step 1: Take 50 ml water in a beaker Step 2:Add sugar in it and stir it Step 3: Nowheat the solution

Step 4: Repeat the process continuously

Step 5: After some time there will be a point at which no more sugar can be dissolved in water. This stage is the saturation point, and the solution is referred to as a saturated solution

Step 6: Now filter the sugar with the help of a filter paper

Step 7: Collect the filtrate in a glass bowl and coolit

Step 8: We will observe that some fine crystals are formed in the bowl

Step 9: The process of filtration can separate these crystals. The liquid left after the removal of crystals is known as mother liquor

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:

(1) The solvent penetrates into the solid matrix;

(2) The solute dissolves in the solvents;

(3) The solute is diffused out of the solid matrix;

(4) 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 intermiscibility (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 phytochemical 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 toohigh, however, may cause solvents to be lost, leading to extracts of undesirable impurities and the decomposition of thermolabile components.

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.

To determine the parameters for effective API desorption from the reference AC material, preliminary experiments were carried out. The approach was evaluated on the two ABC adsorbents after optimization on AC. The APIs were desorbed from the loaded AC and ABCs using a previously described ultrasonication technique that was initially created for use with soil, sediments, and carbon nanotubes (Martn et al. 2010; Mason et al. 2004; Okuda et al. 2009; Wang et al. 2017).

When a liquid or suspension is sonicated, air bubbles are produced, which expand before collapsing. The AC/ABC particles break apart as a result of the shockwaves created by their collapse, increasing the surface area exposed to the extraction solvents (Mason et al. 2004; Yin et al. 2017). Ten extraction solvents were tested, including the nonpolar solvents toluene and dichloromethane (DCM), the polar protic solvent methanol (MeOH), the dipolar aprotic solvent acetonitrile (ACN), and 1:1 binary mixtures of these solvents, because the solvent's polarity and acidity influence contaminant desorption (Martnez-Carballo et al. 2007; Reguyal et al. 2017; (5 mL per extraction). After centrifuging the biochars for 10 minutes at 4700 rpm and sonicating them for 20 minutes at 20 °C, the supernatant was transferred to a 16 mL glass tube and evaporated at 32 °C with an air stream. The APIs were resolubilised with 10 mL of DI water spiked with 10 µL of FA and 26 µL of an internal standard mix containing deuterated ciprofloxacin, sulfamethoxazole, carbamazepine, tamoxifen, promezathine, amitryptiline, oxazepam,risperidone, tramadol, trimethoprim, paracetamol, codeine, flecainide, diclofenac, clotrimazole, and fluconazole. To eliminate the AC/ABC particles, the solution was filtered through a particle filter with a 0.45 m pore size, and the filtrate was then examined using an online solid phase extraction and LC-MS/MS. The APIs were measured in relation to the matching deuterated internal standard for each experiment, which was carried out in triplicate. By taking into account the variations in the starting API concentration, the concentration in the DI water following the 24-hour adsorption, and the outcomes of the extraction, the API's sorption was assessed.

Conclusion :-

Study about the API's Technology For Impurities Avodance , Laboratory Techniques, Experimental Technologies , Impurity Profiling Of API's as well as ICH and Laboratory Safety Guidelines Was studied