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Review Article

Impurity Profiling Of API

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ABSTRACT

This review was written with the intention of gathering the most recent research on floating drug delivery systems (FDDS), with a particular emphasis on the many kinds of FDDS, their principles, and the mechanism of floating to achieve gastric retention. Systems for delivering drugs that float instantly when they come into touch with the stomach With absorption windows in the upper small intestine, fluids offer intriguing strategies for boosting the bioavailability of medications. The most recent developments in FDDS, such as the formulation and physiological aspects that affect stomach retention and techniques for creating single-unit and multiple-unit floating systems, are covered in detail.The goal of the floating drug delivery system (FDDS) is to prolong the period of stomach stay in order to improve bioavailability and therapeutic efficacy.FDDS releases the drug gradually and regulatedly by allowing the dosage form to float over stomach contents with the use of effervescent agents and low-density.

INTRODUCTION

Data evaluation to regulate biological safety of convinced chemicals is known as impurity profiling [1]. As per guidelines set forth by the International Conference on Harmonization (ICH), Anything other than API or excipient that was utilized to make the product is considered an impurity [2]. When it comes to impurity profiling, there is no one, definitive definition. It details the contaminants found in both the raw and processed medicinal products. It is useful for determining the number of contaminants in a pharmaceutical formulation or active pharmaceutical ingredient (API) batch made using a particular controlled production method [3].

Impurities In Active Pharmaceutical Ingredient: Every API needs an impurity profile that details the common and uncommon contaminants found in a batch. In most cases, the API's production method or place of origin dictates the impurity profile. The following types of API impurities are recognized by the ICH as per their guidelines:

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1) Organic contaminants (drug and process-related)
2. Inorganic contaminants
3) Any lingering solvents

1] Organic Impurities:

Medication material is susceptible to organic contaminants that may form throughout production and storage. All of the ingredients, including API, intermediates, degradation products, by-products, reagents, catalyst, ligands, and catalyst, can be volatile or non-volatile, and their identities can vary. Here is how these are explained:

- **Starting materials or intermediates:**

These are utmost prevalent contaminants that can be detected in any API if the multi-step synthesis process is not carried out with the utmost care. Even if solvents are used to wash the final goods, if the producers aren't attentive, there's a potential that some of the unreacted beginning ingredients will remain. Paracetamol can serve as both an intermediary and a starting material for different producers; furthermore, the presence of p-aminophenol in paracetamol bulk can be detected by a limit test. By-products: It is extremely unusual to get a 100% yield in organic chemistry for a only end product; by-products are always a possibility. One of the most prevalent types of process contaminants in pharmaceuticals are by-products from side reactions.

- **Degradation products:**
  Degradation of the final product is another potential source of impurities in bulk medication manufacture. Another prevalent kind of drug impurity is degradation products, which might be a result of storage, formulation into different dosage forms, or simply the passage of time.
- **Products of over-reaction:**

Due to a lack of selectivity in either the final or initial stages of the synthesis, the reagents often attack the intermediate at multiple locations rather than just the one they intended.

Reagents, ligands and catalysts:

These compounds do not typically occur in active pharmaceutical ingredients (APIs), but they can be problematic when present as contaminants. In addition, research has shown that some compounds, such triethylamine, might accelerate the product's degradation.

Impurities originated from reaction solvents:

Impurities can be introduced into the process by certain solvents. Benzene or phenyl derivative friedel-craft acylation frequently employs methylene chloride as a solvent. It is also possible for contaminants to originate from the solvents themselves. tetrahydrofuran is a common solvent for Grignard reagents, although it contains an impurity called 2-hydroxytetrahydrofuran. [4]

- **Enantiomeric impurities**: Because of its superior pharmacological and therapeutic index and reduced side effects, single enantiomeric version of a chiral medication is frequently preferable to the whole molecule. [5]

2] Inorganic Impurities:

They are acquired throughout the production process when drugs are prepared in bulk. In the wild, they're recognized and known. There are a variety of impurities that can be found in various materials, including heavy metals, residual solvents, and filter aids. Chemical substances, ligand, and catalysts It is extremely unusual for us to encounter contaminants of this kind. In the synthesis of linezolid, for example, the use of raney nickel as a catalyst in a reduction reaction had the unintended consequence of producing unwanted byproducts.[6] The catalyst pyridine is employed because pyridinium is produced as an impurity during the production of mazipredone.[7]

- Toxic metals Although water is essential in many industrial operations, it is also a significant contributor to heavy metal pollution. The medication can be hydrolyzed if silver, cadmium,

sodium, manganese, or magnesium are added to the reaction media. As an example, the leaching process causes a significant concentration of metals in the end product when hydrogenated oils and fats are created using metalcatalysts. Demineralized water and reactors walled with glass are utilized for the purpose of testing pharmaceutical products for heavy metal contamination.[8]

Residual Solvents:

These liquids, which can be either organic or inorganic, are commonly employed in a wide range of industrial operations. They pose a threat to human health or alter the characteristics of specific substances. Since some liquids are hazardous, getting rid of them can be a painstaking process because even minute amounts are hard to detect and expel. [9] is cited. Due to their generally volatile nature, gas chromatography is employed for the detection of residual solvents. Through chemical derivatization, nonvolatile solvents are being transformed into volatile solvents. Toluene, acetone, methanol, and dichloromethane may all have their purity and major components quantified using gas chromatographic techniques. [10]

2. Guidelines on impurity [11,12,13,14]

a. Therapeutic Goods Administration (TGA), Australia.
b. US-FDA guidelines: ANDAs -Impurities in New Drug Substances
c. ICH guidelines: Impurities in New Drug Products-Q3B
d. ICH guidelines: Stability testing of new drug substances and products-Q1A
e. US-FDA guidelines: NDAs-Impurities in New Drug Substances
f. ICH guidelines: Impurities in residual solvents-Q3C
g. ICH guidelines: Impurities in New Drug Substances-Q3A

Impurity Detection Method

1. Column Chromatography
2. Separation and Characterization
3. Flash Chromatography
4. GC
5. TLC
6. Capillary electrophoresis (CE)
7. HPLC
8. HPTLC [15]

Analytical Approaches for Impurities

Impurities can be recognized by subsequent diverse approaches.

A. Reference standard technique

Using the basic information provided by the Reference Standard, one can evaluate processes and products, as well as impurities, degradation products, process intermediates, excipients, drug ingredients, and drug products. The overarching goal of this approach is to make the whole process of establishing and overseeing reference standards for the control and development of new medications more transparent.

B. Spectroscopic approaches

In terms of spectroscopy, UV, MS, IR, NMR, and Raman spectroscopy are most popular.[16]

I. UV Visible Spectroscopy

The field known as spectroscopy studies the phenomena that occur when matter interacts with electromagnetic radiation or light. Matter absorbs or emits energy in quanta, which are predetermined amounts. An important occurrence is brought about by this interaction. The materials under study can be better understood through study of absorption and emission processes that take place across whole electromagnetic spectrum, from radio waves to gamma rays [17,18].

Many diverse types of materials can be characterized with help of UV-Vis spectroscopy. Organic molecules and functional groups are examples of inorganic or organic groups that can be seen using UV-Visible spectroscopy. [19]

UV Spectroscopy:

1. Sample Preparation

- Dissolve the sample in a suitable solvent to ensure it's homogeneous and at the appropriate concentration for UV analysis.

2. Baseline Correction

- Run a baseline measurement using the pure solvent to account for any background absorption. This is crucial for accurate readings.

3. UV Spectrum Acquisition

- Use a UV-Vis spectrophotometer to measure the absorbance of your sample across a assortment of wavelengths, typically from 200 to 400 nm.

4. Identify Peaks

- Analyze the spectrum for absorption peaks. Compare the peaks in your sample with the known spectra of pure substances.

5. Quantitative Analysis

- If you know the concentration of certain contaminants, you can use the Beer-Lambert law to measure them.

6. Comparison with Standards

- Compare the absorbance values and peak positions with those of standard solutions or literature values. Deviations can indicate the presence of impurities.

7. Data Interpretation

- Consider the identity and concentration of impurities based on the peaks observed. If unexpected peaks appear, they may represent impurities.
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C. Separation approaches

Some of the chromatographic methods used in this separation process include TLC, HPLC, GC, SFC, and electrophoresis methods such as capillary electrophoresis and gel permeation. [16]

D. Isolation approaches

Subsequent chromatographic systems are used frequently for seclusion of impurities

i. Solid-phase extraction approaches:

This technique separates and isolates the target impurity from a solution by using attraction of solutes dispersed in a liquid and a solid over which sample is passed. Its primary usage is in sample preparation for chromatographic analysis, where the concentration of analytes can be more precisely measured.

ii. Liquid-liquid extraction approaches:

This technique involves dispersing the solute into two different immiscible solvents, such as water and an organic solvent. The partition coefficient or distribution coefficient, which is ratio of the solute concentration in two distinct solvents, was used as the basis for the extraction.

iii. Accelerated solvent extraction approaches:

Rapid (15-25 minutes) extraction of solid and semisolid materials is achieved using this fully automated method, which makes use of common solvents (15-50 ml). ASE uses pressure to maintain solvents in a liquid state during extraction, operating at temperatures above boiling point of the majority of solvents.[21]

II. Column Chromatography:

Based on partition chromatography theory, column chromatography separates the components of the sample as it moves through the stationary phase while being influenced by the mobile phase. Many components elute out based on their affinity for the mobile phase. various rates from the

column under gravity, which results in effective division. Sadly, the speed at which the solvent is very slow as it percolates through the column. The primary advantage of column chromatography is its ability to be sized for the present purpose. In a succession of reactions, this is very helpful for separating and cleaning the reaction mixture. This column may take some time to properly load, which is an additional downside. combine and utilize [22]

III. Thin Layer Chromatography (TLC):

Trace-level chemical identification is possible with the help of TLC. Analytical methods that indicate stability have been developed using this approach. Its downsides are its non-quantifiability and variability. Making the most basic choice all at once is totally doable. It can be used as a quantitative method in conjunction with HPTLC for chemicals that are problematic to analyze using other chromatographic techniques due to lack of a chromophore. Basis for TLC based detection based on interaction of components and a tool for detection. During initial deterioration and stress tests, TLC is heavily utilised to count the amount of degradation products generated [23]

IV. Gas chromatography (GC):

Analytical chemists often employ GC, also known as GLC, to separate and analyze substances that may be evaporated without breaking down. Common applications of GC include determining the concentrations of individual substances or determining the relative concentrations of several components in a mixture. When trying to identify a compound, GC could be useful in certain cases. Use of GC in preparative chromatography allows for the separation of impurities from a mixture. [24] Various articles of study focused on stability stating that there are available GC techniques, for example. identifying divalproex sodium contaminants in pharmaceutical formulations [25], fluconazole [26]

V. High-Performance Thin Layer Chromatography

separates compounds depending on their different empathies to a stationary phase and a mobile phase. This method is predominantly useful for analyzing complex mixtures and detecting impurities.

VI. High Performance Liquid Chromatography (HPLC):

HPLC is a flexible analytical tool since it can be used with both volatile and stable samples; the technique relies on the fact that different chemicals migrate at different speeds on various stationary and mobile phases to separate them [27]. part separation by means of HPLC with an appropriate detector, for example, a PDA detector [29], a refractive index detector [28],” The use of fluorescence, electrochemical, electrical conductivity, light scattering, evaporative light scattering, Corona Charged Aerosol Detector (CAD), Nano Quantity Aerosol Detector (NQAD), and other detectors allows for the quantitative analysis of pharmaceutical products and impurities in a precise, accurate, and dependable manner. The stability of both the pure drug material and drug formulations can be monitored using HPLC. One example of a breakdown product is salicylic acid, which can be measured in diprosalic lotion using a stability-indicating method and HPLC. Related compounds include norfloxacin [31], allantoin [32], and betamethasone dipropionate [30].

VII. Capillary Electrophoresis (CE):

It is a method of separation that uses the electric field's effect on the relative sizes of charges in a conductive material to achieve separation. Ions travel quicker in an electric field when the ratio is greater. One of the most promising approaches to ion separation is.[21]

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