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Original Article

Significance of Formulation Development and Packaging Controls: Research on Product Integrity/Quality

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ABSTRACT

Background: The pharmaceutical Industry is one of the sectors with the most stringent guidelines since it deals with human lives. Faults in the manufacturing of pharmaceutical products provide serious obstacles to assure quality safety and efficacy. Defective product is the one that lacks or fails to meet consumer's needs and may pose some risk if used. A pharmaceutical firm would face a few repercussions if such a defective product were to be launched onto the market. Even with GMP procedures and SOPs in place, regulatory authorities still identify manufacturing flaws in marketed brand or generic medications and errors and wrongdoing by pharmaceutical companies, which eventually result in product recalls. Customer complaints and product recall cases were evaluated to determine the clinical importance of these flaws. The objectives of the study were to investigate quality problems associated with amino acid-based pharmaceutical products that were gathered from the hospital pharmacies and retail establishments and perform a visual examination of the likely underlying cause of the defect, corrective actions, and measures, also determine the clinical importance of each identified defect. This research emphasizes safeguarding patient safety and raising awareness of product quality, thus minimizing manufacturing defects in pharmaceutical products. **Materials and Methods:** The study involved identifying the defects, categorizing the type of defect and its fundamental root causes, and suggesting remediations. It captured the clinical importance of the defective dosage forms and listed the lessons learned from the study. The dosage forms included Parenteral preparation and tablets prescribed for their specific therapeutic activity. **Results:** The investigation has identified minor, major, and critical quality concerns. These flaws were distinct in character and seemed to be distinct instances that weren't even mentioned in conventional literature or textbooks. **Conclusion:** Pharmaceuticals are vital assets for treating diseases, and their quality shouldn't ever be compromised because it may considerably affect the medication's efficacy and safety. To maintain this, an attentive and dedicated quality assurance staff and close adherence to the established rules by regulatory authority are needed. This strategy puts patient safety first and ensures the supply of high-quality medications.

Keywords: Manufacturing defects, Recalls, Quality control, Packaging.

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INTRODUCTION

Drugs can be incorporated into the human body through different anatomical routes. They may be targeted towards specific organs and illnesses. The choice of the route of administration depends on the disease and the desired effect. Pharmaceutical drugs can be administered systemically and targeted towards the diseased organ or directly to the organ that is affected.[1] Pharmaceutical dosage forms include various formulation delivery platforms designed to enhance patient acceptance and bioavailability.[2] Tablets and capsules are often preferred means of oral administration since they are patient-friendly and most practical for self-administration of medication. Injectable formulations are developed to treat patients for immediate effect or in an emergency where the patient might not be able to take oral medication due to unconsciousness.[3] The primary focus of formulating the drug in a dosage form is to achieve a consistent

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therapeutic response, which can then be manufactured on a large scale with consistent product quality.[4]

Before formulating a drug substance into a dosage form, multiple factors are taken into consideration, these are mainly grouped into three categories:

- Biopharmaceutical considerations, including factors affecting the absorption of the drug substance from different administration routes.
- Drug factors, such as the physical and chemical properties of the drug substance.
- Therapeutic considerations include the clinical indication to be treated and patient factors.[4]

Amino acids are simple chemical, organic compounds with one or more amino groups and carboxyl groups. They are the building blocks of proteins, peptides, and other complex polymers, such as the cell wall.[5] Drugs developed using amino acids are often less toxic, have strong metabolic and pharmacokinetic characteristics, a significant bioavailability and permeability, and a modest potency.[6] The type of protein synthesized depends on the kinds of amino acids involved and the order in which they are organized. The most researched issues in biological research are amino acids and their importance for metabolism and physiology. A wide range of research has been done on the therapeutic uses of amino acids in respiratory physiology, cardiology, renal failure, neurological illnesses, and congenital abnormalities.[6]

Recalls

"Recall" represents the action of taking a faulty or possibly hazardous product off the market. Recalls can be voluntary initiatives started by the manufacturer or mandatory actions enforced on the manufacturer by regulatory bodies. A recall can be started by a manufacturer on his own or in response to a formal request or order from the agency, or upon notification from regulatory bodies. The primary objective of the recall process is to strengthen consumer protection and improve health system (Table 1).[7,8]

Classification of recalls[7,8]

Class 1

A situation when there is a reasonable chance that taking a controlled substance might cause serious health issues or sometimes possible death in the public.[9]

Examples

- Defective items with significant adverse health effects.
- Severe health risks caused by chemical contamination.
- Microbially contaminated sterile and ophthalmic medications.

Class 2

Whenever a product problem has the potential to cause sickness or abuse, it is not a Class I problem.

Examples:

- Labelling error.
- Incorrect information in leaflets and medical literature.
- Not adhering to specifications in relation to assay, stability, testing, or weight, which leads to a negative impact on health.
- Non-sterile and non-ophthalmic with microbiological contamination.

Class 3

A circumstance where using a prohibited substance doesn't have a significant negative impact on individual's health.

Examples

- Inappropriate packing.
- Failing to include batch number and product number.
- Substandard closures that don't have any adverse medical consequences.
- Contamination with no medical consequences products such as.
- Microbial spoilage, Dirt, Particulate matter.

CASE STUDIES

Case Study 1 - Investigation of discoloured I.V Injection vial

Dosage form: I.V Injection vial.

Generic Name: Amino acids I.V infusion.

Therapeutic category: Used as nutritional support, as well as treatment of negative nitrogen balance in blood.

Defects: Discoloration of amino acid parenteral solution (Figures 1a and 1b).

Category of complaint: Critical.

Probable root causes

➢ Amino acids have different pKa values, and improper pH can lead to precipitation, reduced solubility, or degradation.

➢ Insufficient Buffering agent or stabilizing agent.

➢ Fluctuations in storage temperature result in degradation of the IV solution.

➢ Exposure of the solution to light due to absence of light sensitive packaging or ambered coloured bottles.

➢ Leaching effect from the glass containers.

➢ Improper purging of nitrogen during the pre-filling process.

Remediation

➢ Store and transport the IV solutions under optimal temperature conditions (e.g., refrigerated or ambient) based on the stability profile of the solution.

➢ For light-sensitive solutions, use light-resistant containers (e.g., amber glass or coated plastic) to prevent photodegradation.

➢ Packaging materials that are compatible with the amino acid solution, preventing leaching.

Clinical significance

Therapeutic concentration may not be achieved and thus efficacy is reduced. Adverse events due to toxic substance may appear. Degraded IV fluid may lead to systemic infections and other complications.

cGMP Learnings

- Camera and alarm-based systems can be implemented if manual inspection fails.
- The line-in-charge of the respective department should ensure that line clearance is done correctly and in accordance with cGMP requirements.
- Conduct final product inspections to detect foreign particles/degradation before distribution.
- Proper stability studies should be carried out for each batch.
- Closures on the parenteral products should be properly sealed and a leak test must be performed.
- Follow ICH Q1A-Q1F stability guidelines.
- Maintain the packaging integrity of the product

Case Study 2: Investigation of melted/softened tablets

Dosage form: Film-coated Tablets.

Generic Name: Ketoanalogues and Essential amino acid tablets.

Therapeutic category: Treatment of CKD.

Defects: 3 tablets were found to be melted/softened within the intact blister packing (Figures 2a and 2b).

Category of complaint: Critical.

Probable root causes

Formulation-Related Causes

➢ The core of the tablet is not properly compressed because of, which it can lead to cracking or peeling during the coating.

➢ Incompatibility of excipients like fillers, binders, and plasticizers with the coating solution leads to poor adhesion, mottling, and other defects.

➢ If the quantity of plasticizer is low, the coating becomes brittle, leading to quality defects during storage.

Environmental causes

➢ Hygroscopic ingredients absorb moisture, which can lead to chemical degradation and tablet softening.

➢ Heat, light, and oxygen sensitivity of amino acids like tryptophan and methionine.

Handling and storage

➢ Storage of tablets in high humidity or extreme temperatures can degrade the tablet and film coating.

➢ The packaging does not provide enough protection against light, temperature, and moisture.

➢ Tablets are packaged in transparent or insufficient opaque materials.

➢ In the process Quality check was not done adequately.

Remediation

➢ A strict supplier qualification program to assess and approve raw material suppliers based on their compliance with quality and safety standards.

➢ Adhere to SOPs for production, packaging, labelling, and storage.

➢ Regularly monitor each production batch to ensure the formulation is stable and consistent between the batches.

➢ Maintain cleanroom environments and, check for microbial contamination and validate.

➢ Compression force monitoring to ensure the tablet core is neither too hard nor soft.

➢ Validate packaging processes to ensure that the packaging material protects from moisture, oxygen, and light.

➢ Packaging materials that are impermeable to moisture, especially for hygroscopic products.

➢ Use opaque or UV-blocking packaging materials to protect against photodegradation.

Figure 1(a): Upright position of the defective product.

Figure 1(b): Inverted position of the defective product.

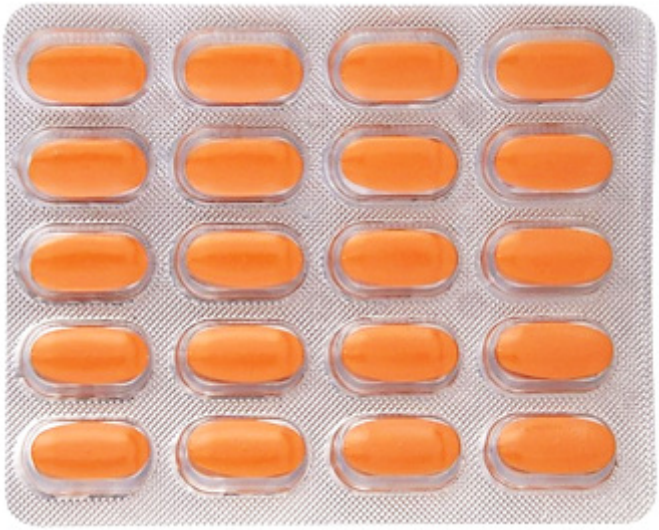

Figure 2(a): Good Film-coated tablet.

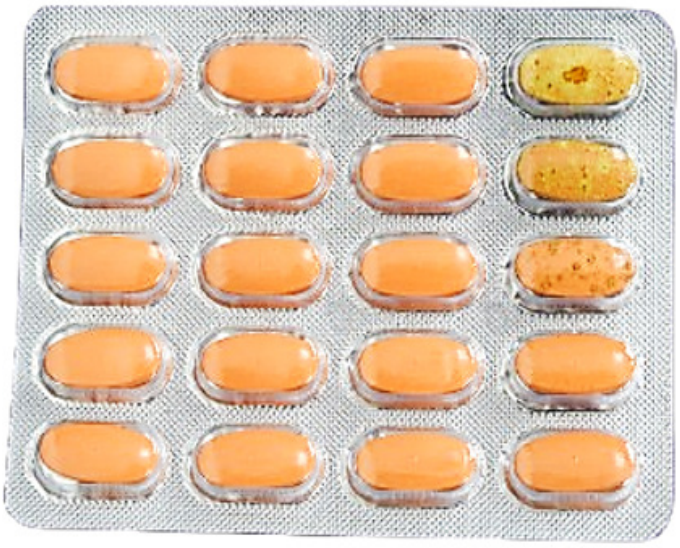

Figure 2(b): Defective Film-coated tablet.

➢ Nitrogen-flushed packaging to minimize exposure to oxygen.

➢ By using PVC and PET combined aluminium blister packs.

Clinical significance

The API of the product might undergo degradation due to the influence of light and moisture, which may increase the adverse effects. The release profile of the drug may be altered, which might result in variations in the drug's bioavailability. The patient may not be able to receive the required dose to show pharmacological activity.

cGMP LEARNINGS

- Most of the amino acids are sensitive to moisture and light. Therefore, they have to be completely sealed and packed in moisture and light-sensitive packaging materials.
- Validate packaging process.

Table 1: List of Recalls of Drug Product (Figures 3 and 4).[9]

Date	Product Description	Reason for recall	Company Name	Class of Defect	Class of Recall
06-05-2024	STELLALIFE VEGA Oral Care, Spray,	Microbial contamination	Homeocare Laboratories, Inc.	Critical	Class I
08-05-2024	Rubbing Alcohol, First-Aid Antiseptic,	cGMP Deviations	Zeco LLC	Major	Class II
09-05-2024	Pyridoxine HCL (B6) Injection Solution	Lack of assurance of sterility	Empower Pharmacy	Major	Class II
16-05-2024	Estradiol Transdermal System, USP	Failed impurities	Zydus Pharmaceuticals (USA) Inc	Minor	Class III
17-05-2024	Dolutegravir Tablets for Oral Suspension	Labelling Error	GlaxoSmithKline LLC	Minor	Class III
22-05-2024	Eptifibatide injection, Single dose vial	Failed impurities	Eugia US LLC	Minor	Class III
28-05-2024	Docetaxel Injection, Multi-dose vial	Presence of foreign substance	Sagent Pharmaceuticals	Critical	Class I
05-06-2024	Metoprolol Tartrate Tablets	Presence of foreign substance	Rubicon Research Private Limited	Major	Class II
08-06-2024	IBU Ibuprofen Tablets, 800 mg	Failed impurities	Dr. Reddy's Laboratories, Inc.	Major	Class II
08-06-2024	IBU Ibuprofen Tablets, 600 mg	Failed impurities	Dr. Reddy's Laboratories, Inc.	Major	Class II
08-06-2024	IBU Ibuprofen Tablets, 400 mg	Failed impurities	Dr. Reddy's Laboratories, Inc.	Major	Class II
24-06-2024	Decongestant (oxymetazoline HCl) Nasal Solution, Nasal Decongestant	Sub potency	Neilmed Pharmaceuticals Inc	Minor	Class III
24-06-2024	Diflorasone Diacetate Ointment	Failed impurities	Rising Pharma Holding, Inc.	Minor	Class III
26-06-2024	Sevelamer Carbonate for Oral Suspension	Labelling error	Dr. Reddy's Laboratories, Inc.	Minor	Class III
05-07-2024	Triamcinolone acetonide extended-release injectable suspension	Failed stability	Pacira pharmaceuticals inc	Major	Class II
05-07-2024	Losartan Potassium and Hydrochlorothiazide Tablets	Presence of foreign substance	Macleods pharma USA, inc	Major	Class II
06-07-2024	Allopurinol Tablets, USP 300mg	Presence of foreign substance	Dr. Reddy's Laboratories, Inc.	Major	Class II
06-07-2024	Daily Moisturizing Body Lotion, 1.3% Dimethicone	Microbial contamination	Brands International Corporation	Major	Class II
08-07-2024	Hydrocortisone 1% and Acetic Acid 2% Otic Solution	Failed impurities	Taro Pharmaceuticals U.S.A., Inc.	Minor	Class III
18-07-2024	Acetaminophen, USP 500mg, Pain Reliever/Fever Reducer, Extra Strength, Rapid Release Gelcaps	Labelling error	Granules Consumer Health Inc.	Minor	Class III
04-08-2024	Sapropterin dihydrochloride Powder for Oral Solution	Sub Potency	Dr. Reddy's Laboratories, Inc.	Critical	Class I

Date	Product Description	Reason for recall	Company Name	Class of Defect	Class of Recall
05-08-2024	Cefdinir for Oral Suspension	Defective container	Lupin Pharmaceuticals Inc.	Major	Class II
07-08-2024	Acetaminophen Injection Single Dose bags for Intravenous	Labelling error	Hikma Pharmaceuticals USA Inc.	Critical	Class I
08-08-2024	Testosterone gel, unit-dose packets	Super potency	Teva Pharmaceuticals USA, Inc	Major	Class II
07-09-2024	Nitrofurantoin Capsules,USP (Macrocrystals).	Failed dissolution	SUN PHARMACEUTICAL INDUSTRIES INC	Major	Class II
10-09-2024	Cinacalcet Tablets	cGMP Deviations	Dr. Reddy's Laboratories, Inc.	Major	Class II
30-09-2024	Ciclopirox Gel 0.77%, For Dermatologic Use Only, Not for Use in Eyes	Defective container	Glenmark Pharmaceuticals Inc., USA	Minor	Class III
05-10-2024	Rizatriptan Benzoate Tablets USP	cGMP Deviations	Glenmark Pharmaceuticals Inc., USA	Major	Class II
05-10-2024	Cephalexin tablets for Oral Suspension	Labelling error	Bryant Ranch Prepack, Inc.	Minor	Class III
07-10-2024	Clonazepam Orally Disintegrating Tablets	Labelling error	Endo Pharmaceuticals, Inc.	Critical	Class I
10-10-2024	Cinacalcet Tablets	Failed impurities	ACCORD HEALTHCARE, INC.	Major	Class II
10-10-2024	Duloxetine Delayed-Release Capsules 20mg	cGMP Deviations	Breckenridge Pharmaceutical, Inc	Major	Class II

- Ensure GMP-compliant storage conditions like temperature and humidity control.
- Products have to be adequately sealed in order to make sure that environmental factors lead to degradation of the factors.
- Perform rigorous quality check.

TECHNICAL SUMMARY

Degradation pathways of Amino acids

Chemical degradation pathways

Hydrolysis

Hydrolysis is the primary pathway of amino acid degradation which is highly dependent on pH. Under normal biological conditions and extreme acidic pH, amino acids such as asparagine and glutamine undergo deamidation through direct hydrolysis and acid catalysed direct hydrolysis to form aspartate and glutamic acid.[10-12]

Oxidation

The oxidation reaction is a phenomenon that increases the electronegative atom content. Due to the high reactivity of Sulphur atoms, Sulphur-containing amino acids such as methionine and cysteine readily lose electrons and undergo oxidation to produce Sulphur radicals when exposed to reactive oxygen species. Aromatic rings containing residues such as histidine, tryptophan, and tyrosine are prone to oxidation due to the presence of multiple carbon-carbon double bonds that are easily oxidized by various ROS. Oxidation can be caused by multiple materials like trace amounts of catalytic redox active metals, light exposure. Also, pH, temperature, and buffer composition may impact peptide oxidation.[12]

Metal induced Oxidation

Metal ion catalyzed oxidation of peptides usually requires redox-active transition metals such as Fe^{2+} and Cu^{2+}, which may participate in redox cycling processes and generate ROS, which is normally required for this process to occur. The ions in metal ion-catalyzed oxidation act as a catalyst, thus speeding up the conversion of hydrogen peroxide, superoxide anion radicals, and hydroxyl radicals. Drugs with residues of amino acids like Histidine (His), Cysteine (Cys), and Methionine (Met) are susceptible to oxidation by metal ions. Oxidation mediated by metal ions is a site-specific process that involves the formation of complexes with metal-binding sites. Histidine and methionine undergo metal induced oxidation to form sulfoxide and imidazole-aldehyde products.[12,13]

Photo oxidation

Peptides with disulfide bonds or aromatic amino acid residues such as tyrosine, phenylalanine, and tryptophan are often susceptible to undergo light-induced oxidation. The processes underlying light-induced oxidation are intricate and poorly understood. Although the fundamental photo physics and photochemistry of tryptophan, tyrosine, phenylalanine, and cystine have received a lot of attention, secondary reactions can result in the creation of a wide range of compounds. The irradiation of light on tryptophan can cause photoionization as well as the generation of singlet oxygen. This electron release during photoionization can react with electronegative atoms such as oxygen to produce superoxide or disulphides (thiolate and thiyl radical).[12]

Physical degradation pathways

Aggregation

Mostly, the aggregation phenomenon is seen during the storage of drug products. Amino acid aggregation in the solid state can be classified as noncovalent or covalent. In non-covalent aggregation, partly denatured amino acids associate intermolecularly via hydrophobic interactions with one another to reduce the unfavourable exposure of hydrophobic amino acid residues to water whereas covalent aggregation involves the formation of chemical bonds like as dityrosine, ester, disulfide, amide linkages, electrostatic interactions or non-covalent bonds through hydrophobic interactions.[14] Several concurrent mechanisms can occur simultaneously, leading to the formation of soluble and insoluble aggregates. When amino acids aggregate, there is a change in size, solubility, bioavailability, and biological activity. At elevated concentrations of amino acids, they establish

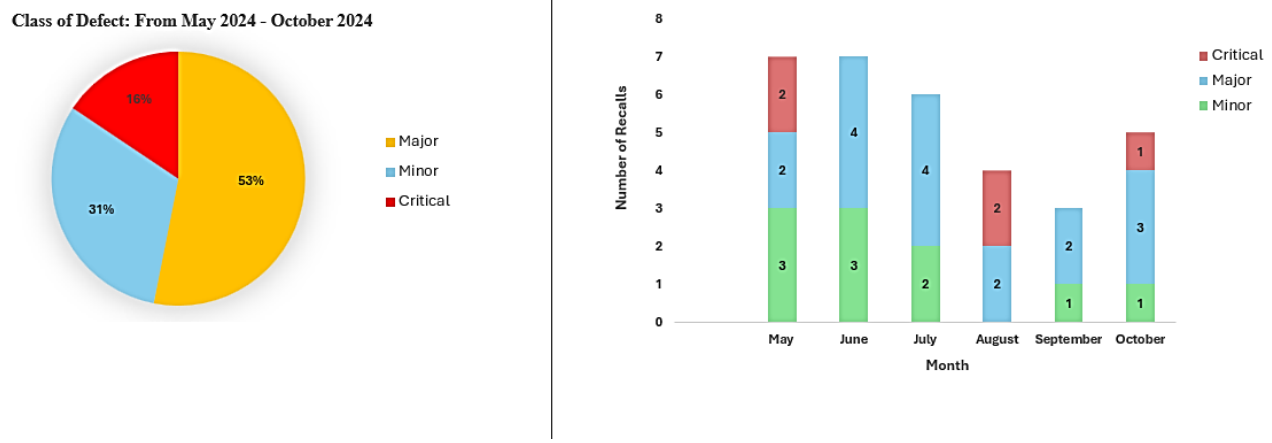

Figure 3: Distribution and Monthly Trends of Defect Classes from May 2024 to October 2024.[9]

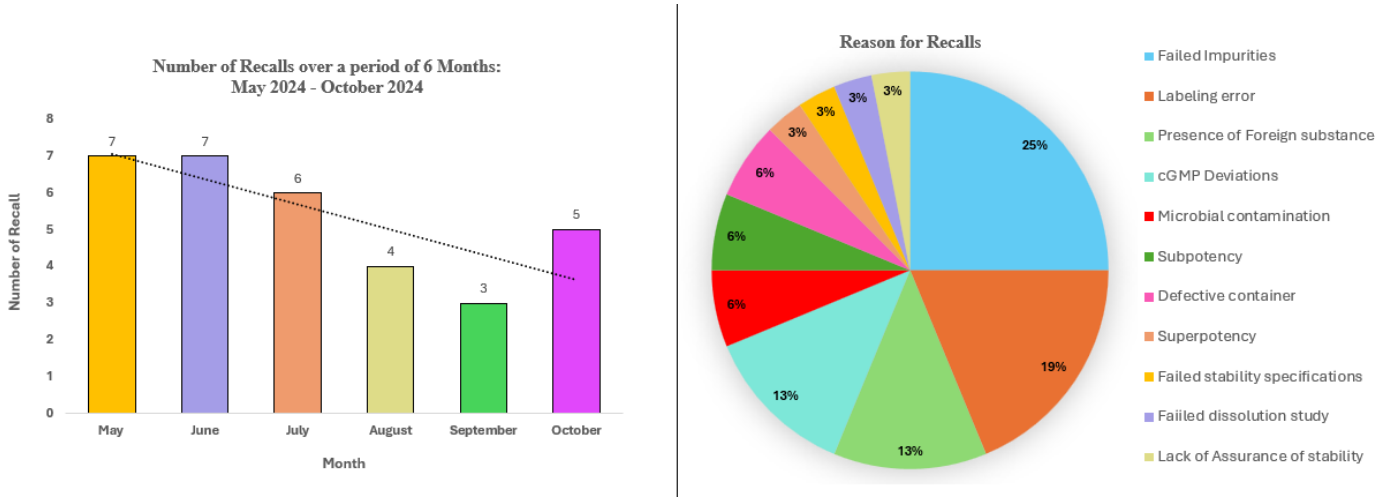

Figure 4: Monthly Recall Trends and Distribution of Root Causes May 2024 to October 2024.[9]

stronger intermolecular interactions, leading to accelerated aggregation. As this aggregation continues, the amino acids may become insoluble and precipitate, occasionally forming gel-like aggregates.[12,15]

Adsorption

Proteins are naturally amphiphilic polyelectrolytes, due to which they have a certain amount of surface activity that causes them to adsorb to surfaces. Proteins can adsorb during the manufacturing, storage, or usage of a finished product, lowering or eliminating the biological activity and serving as a precursor to aggregation, denaturation, and precipitation.[16] Adsorption process is affected mainly by temperature, pH, ionic strength of the medium, and the nature of the surface.

Factors influencing instability of amino acids

Temperature

When formulations containing amino acids are exposed to high temperatures, almost all chemical breakdown processes are accelerated, typically reducing chemical stability. Amino acids, like cysteine, when exposed to high temperatures, undergo inactivation due to the breakage of disulfide bonds through beta elimination. It has been noted that the rate of covalent cross-linking in the solid state increases with temperature. An increase in temperature accelerates most degradation processes like oxidation peptide bond breaking, Maillard reaction, and deamidation. The cause for temperature-based chemical instability may be due to mobility in the system or lowering of the activation barrier for response.[17]

Moisture

Water can be in bound or unbound form. The bound water is the water of hydration or crystallization that is firmly integrated into the material's physical form that is practically immobile and not available for reactions. On the other hand, unbound water often has better molecular mobility and is in equilibrium with the atmosphere when it is absorbed or adsorbed by the solid components.[18] Residual moisture is usually thought to be responsible for protein and peptide chemical instability in the solid state. Formulations consisting of lyophilized proteins are more stable when the water content is less. Water concentration has a significant impact on the covalent aggregation of amino acids in the solid state. The ability of freeze-dried amino acids to undergo aggregation in a moistened solid state is greater than in a solution. A bell-shaped relationship exists between the water content and covalent aggregation. The degradation process is accelerated when molecular mobility is increased due to higher water content. Increases in headspace oxygen was shown to have an impact on a lyophilized formulation's oxidation at low moisture contents but not at higher moisture contents. This might be because water has potential antioxidant qualities. Depending on the system, water can be an oxidant or an antioxidant.[17]

pH

pH is used as a simple indicator of hydrogen ion activity. To understand relative protein stability, pH-stability experiments are carried out during the early phase, typically from pH 3 to about pH 10. In general, solubility and stability relation follow this pattern: Lower solubility results in lesser physical stability, whereas higher solubility leads to poorer chemical stability. Protein solubility often reaches its lowest value at its isoelectric point.[16,17] Elevated pH levels might potentially assist in the binding of metal to amino acid residues, resulting in the ionization of the side chain functional group, thus facilitating metal-induced oxidation.

Light

Several protein pharmaceuticals can undergo oxidative changes during storage due to their high sensitivity to light. The accelerated stability of photosensitive protein medicines is performed by exposing UV light in a light chamber. Light-induced oxidation is frequently seen during the processing and storage of proteins, but the types of photoreactions and the nature of the reactive intermediates involved are not well understood. Amino acid residues like Tryptophan, tyrosine, phenylalanine, and cystine are known to absorb in the near-UV spectrum. In the near-UV range, tryptophan has the greatest absorption, followed by tyrosine.[12]

Impact of recalls on pharmaceutical companies and public health

Drug product recalls can significantly impact different segments of the pharmaceutical business like market share, corporate science, public health, supply chain, and distribution. This may create a belief that the pharmaceutical industry is unreliable in maintaining a high standard of quality of drug products and is engaged in fraudulent activities. Pharmaceutical companies collaborate with other businesses for the manufacturing of drug products, like third-party involvement and loan licensing systems. It might be challenging to trace the precise cause of the defect in the product since a large number of parties are involved. Pharmaceutical recalls can have serious repercussions for public health systems. The direct impact is on the patients who might suffer negative responses, adverse drug reactions, or no effect as a result of defective products. These circumstances may interfere with essential treatment regimens, causing diseases to worsen or interrupt critical health care. Healthcare providers are also severely impacted by recalls, involving a significant amount of time and resources to handle the repercussions, from calling patients to offering substitute therapies. A drug product recall can put customers in doubt and confusion about whether they must continue taking the recalled prescription or switch to an alternative.[19,20]

CONCLUSION

Irrespective of the product type, no individual prefers to buy a faulty product or anticipates any quality problems. Substandard quality of medicines is due to the incompliance of pharmaceutical industries to Standard Operating Procedures (SOPs) and regulatory bodies. Defects result in product recalls, which have an impact on a brand's reputation and can have economic consequences. Defects can be avoided by properly training personnel, adopting modern machinery, automating processes, determining the root causes for product defects, and thoroughly inspecting them before they are released into the market. The defects addressed in this article could benefit pharmaceutical industries by helping them understand the kinds of problems that could arise and take appropriate remedies to avoid them in the future. Each personnel in the pharmaceutical industry who is dealing with the drug product, starting from API manufacturing to the packaging of the drug product, must be held accountable for the quality of the product, thus safeguarding the patient's safety and reliability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GMP: Good Manufacturing Practices; **SOPs:** Standard Operating Procedures; **IV (I.V):** Intravenous; **cGMP:** Current Good Manufacturing Practices; **CKD:** Chronic Kidney Disease; **UV:** Ultraviolet; **PVC:** Polyvinyl Chloride; **PET:** Polyethylene Terephthalate; **ROS:** Reactive Oxygen Species; **API:** Active Pharmaceutical Ingredient.

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ETHICAL APPROVAL/STATEMENT

This is conducted as a part of the student education, and we have ensured that both brand name and company name are masked. Since it is focused only for education, ethical approval is not applicable.

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