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Review Article

Pharmaceutical Excipients: Functions, Selection Criteria, and Emerging Trends

Saniya Makkad*, Mujibullah Sheikh, Sanskruti Shende, Pranita Jirvankar

Department of Pharmacology, Datta Meghe College of Pharmacy DMIHER (Deemed to be University), Wardha, Maharashtra, INDIA.

ABSTRACT

Pharmaceutical excipients are integral to therapeutic formulations; their importance has grown from inert and economical materials to components that make up 80-90% of the finished product. This review examines the excipient classification scheme developed by the International Pharmaceutical Excipient Council (IPEC) and the process by which safety evaluation criteria are set for newly suggested excipients. It also highlights how excipients impact the price, effectiveness, and stability of medications, especially when used in solid dosage forms. The study also addresses new developments in excipient functionality and utilization, highlighting the need for multifunctional excipients to improve pharmacological efficacy, stability, and affordability. The purpose of this article is to shed light on the roles that pharmaceutical excipients play in the efficacy of medication formulations by examining their functions, selection criteria, and developing trends.

Keywords: Pharmaceutical Excipients, Formulations, Active pharmaceutical ingredient (API), Excipient selection, Interactions.

Correspondence:
Ms. Saniya Makkad
Department of Pharmacology,
Datta Meghe College of Pharmacy
DMIHER (Deemed to be University),
Wardha-442001, Maharashtra, INDIA.
Email: makkadsaniya@gmail.com

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INTRODUCTION

Pharmaceutical excipients are crucial parts of medicine formulations and are important to the creation and production of drugs. They are described as ingredients added to the formulation to ensure the quality, safety, and efficacy of formulations, aside from the Active Pharmaceutical Ingredient (API). Excipients have the potential to facilitate drugs solubility, increase stability, boost bioavailability, and maintain dose homogeneity. Additionally, they support the drug delivery system's general efficacy and safety. As a matter of fact, 90% of recently identified therapeutic compounds and 40% of currently available pharmaceuticals have low water solubility, emphasizing the critical role that functional excipients play in addressing these barriers (Van der Merwe J *et al.*, 2020). Excipients are crucial in many aspects of the production of pharmaceuticals. ensuring the security, efficacy, and caliber of pharmaceuticals is their primary responsibility. Excipients help to increase the quantity of medication that is bioavailable and improve the solubility of pharmaceuticals that are not highly soluble in water, all while aiding in the delivery mechanism for APIs. They also have an important part to play in the manufacturing process, helping to identify the drug product and disintegrate the drugs (Available from). Excipients can be added to the formulation to improve the drug's physico-chemical qualities or to aid in its dissolution. Additionally, they can be utilized to re-formulate already-existing drugs to create more potent medications and to create dosage forms that can decrease the number of doses by enhancing drug delivery. Excipients are typically added to dosage forms in larger amounts than the Active Pharmaceutical Ingredient (API) and are involved in every facet of the finished product, such as the API's stability, dose consistency, efficient delivery to the systemic circulation following administration, and appropriate patient compliance (Patel R *et al.*, 2020).

Functions

Pharmaceutical excipients play several crucial roles in drug formulations. Keeping liquid formulations at the proper pH and/or osmolarity is just one of these responsibilities; additional responsibilities include regulating the solubility and bioavailability of APIs, stabilizing APIs in the dosage form, encouraging patient acceptability, helping with product identification, and improving the overall safety and efficacy of the drug delivery system. Excipients play a crucial role in the manufacturing process and the efficacy of drugs, making them necessary components in contemporary pharmaceutical supplies. They can be used as preservatives, coloring agents, lubricants, binders, disintegrants, and diluents. Excipients can also help to facilitate formulations and improve the functionality of products. As these functions demonstrate, excipients play a crucial role in providing the

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effectiveness, safety, and overall quality of pharmaceutical formulations (Elder DP *et al.*, 2016).

Increasing Stability: Excipients contribute to the shelf life of a drug product by assisting to keep Active Pharmaceutical Ingredients (APIs) stable in the dosage form.

Modulating Bioavailability and Solubility: Excipients can improve the body's solubility and bioavailability of APIs.

Preserving Osmolarity and pH: Excipients assist in maintaining liquid formulations' pH and osmolarity, ensuring their compatibility with the physiological conditions of the body.

Improving Patient Acceptability: By making the drug product taste better and look better overall, they increase patient acceptability and encourage compliance, especially in younger patients.

Helping with Product Identification: A few excipients facilitate the drug product's identification.

Ensuring Safety and Effectiveness: To improve the formulation's overall safety and effectiveness, excipients are added to drug delivery systems (Van der Merwe J *et al.*, 2020).

Excipients are inert materials that are added to drugs to facilitate drug dissolution, absorption and delivery. They can be introduced to the formulation in order to assist the drug dissolution, or specific dosage forms that increase the rate of dissolution through different methods can be created. Excipients can influence how quickly a solid dosage form dissolves, and some can even adsorb Active Pharmaceutical Ingredients (APIs), improving bioavailability in the process. Pharmaceutical excipients have a variety of functional roles, such as regulating bioavailability and solubility, boosting API stability in the dosage form, preserving the liquid formulations' osmolarity and/or pH, averting dissociation and aggregation, etc, (Li Z *et al.*, 2021).

Classification of Excipients

Based on their origin

- Animal source- Beeswax, honey, lanolin, stearic acid, lactose.
- Vegetable source- Starch, acacia, peppermint, turmeric, and guar gum.
- Mineral source- Calcium phosphate, kaolin, asbestos, silica, calamine, talc, paraffin.
- Synthetic source- Polyethylene glycols, polysorbates, lactic acid, boric acid, and saccharin.

Based on Function

Binders, Surfactants, Emulsifying agents, Disintegrants, Lubricants, Cosolvents, Fillers Sweeteners, Flavors, Glidants, Colors, Preservatives, Film coatings, Dispersing agents, Printing inks, Compression aids.

Based on Role in Pharmaceutical Formulation

Antioxidants, Coating materials, Emulgents, Taste and smell improvers, Ointment bases, Conserving agent, Consistency improvers.

Selection criteria of excipients

The ideal properties of pharmaceutical excipients are critical for ensuring the effectiveness and purity of pharmaceutical dosage forms, and they perform a significant role in drug formulations. Excipients should ideally modulate bioavailability and solubility, prevent aggregation and dissociation, maintain the pH and osmolarity of liquid formulations, and improve the stability of APIs in the dosage form. Furthermore, excipients should overcome low drug bioavailability, promote drug dissolution, and improve wettability. The stability and efficacy of the medicinal product might be significantly affected by the excipients' properties and concentration (Patel R *et al.*, 2020). High-functionality excipients are especially useful since they are capable of performing a variety of tasks, including enhancing flow, serving as a disintegrant, and enabling an increased drug loading. Pharmaceutical technology is also focusing on the creation of multifunctional excipients, or substances that can operate as both a binder and a direct-compressible filler material at the same time. Excipient stability is a crucial factor to take into account since it affects the quality and performance characteristics of pharmaceutical dosage forms. In order to ensure the dosage form's physical and chemical integrity as well as the packaging's integrity, excipient stability is crucial (Pockle RD *et al.*, 2023).

Excipients should be studied in terms of interactions and possible ways to mitigate instabilities, in addition to their direct impacts. Excipients are vital for the preservation of products because they protect the Active Pharmaceutical Ingredient (API) from external influences and alter sensory attributes like appearance, texture, taste, and smell. Comprehending the fundamental standards of excipients, the rationale behind the creation of novel excipients, and the varieties of excipients that are now in use are essential for the continuous progression of pharmaceutical compositions (Pockle RD *et al.*, 2023).

Drug development logically depends on the selection of excipients, that serve as essential components of pharmaceutical formulations. Excipient selection involves a number of considerations, such as functionality, compatibility, safety, and regulatory requirements. Dosage forms consist of excipients to improve the solubility, stability, efficacy, and safety of drug, Additionally, they can be utilised as tonicity or bulking agents, or they can assist in the controlled delivery of drugs. It is critical that excipients be thoroughly proven safe before being used in pharmaceutical formulations. The target population, mode of

Table 1: Excipients used in tablets.

Excipient	Use	Examples	References
Diluents	These are fillers that are added to tablets to increase their volume. They can also modify the release rate of the drug.	Calcium carbonate, dibasic calcium phosphate, Calcium sulfate, dextrose, lactose, mannitol, starch etc.	(Van der Merwe J *et al.*, 2020)
Binders	They give powdered materials cohesive strength and serve as binding agents in tablets.	Acacia, carbomer, gelatin starch, cellulose, Hydroxypropyl cellulose, Povidone etc.	(Van der Merwe J *et al.*, 2020)
Disintegrants	These facilitate the tablet's disintegration into smaller components	Alginic acid, cellulose, guar gum, Sodium alginate, sodium starch glycolate etc.	(Available from)
Lubricants	Used to reduce the friction that presses the tablet against the die wall, keeping it from adhering to dies and punches.	Calcium stearate, Fumaric acid, Sodium lauryl sulfate, magnesium stearate and stearic acid.	(Patel R *et al.*, 2020)
Glidants	Used to enhance the flowability of powder or granules.	Calcium silicate, Magnesium oxide, Magnesium carbonate, Starch, Talc etc.	(Available from)
Preservatives	They prolong the product's shelf life and prevent microbiological growth.	Benzalkonium chloride, propyl paraben, methylparaben etc.	(Elder DP *et al.*, 2016)

Table 2: Excipients used in liquid dosage forms.

Excipient	Use	Examples	References
Solvents	For dissolution of API or other excipients.	Alcohol, water, syrups, ethyl acetates, acetone, acetic acid, etc.	(Elder DP *et al.*, 2016)
Cosolvent	Increases the solubility of drugs in solvents.	Propylene glycol, glycerin, ethanol etc.	(Li Z *et al.*, 2021)
Buffering agents	Maintain the pH of the formulations.	Citric acid, phosphate buffers, and acetate buffers etc	(Li Z *et al.*, 2021)
Preservatives	Prevent the growth of microbes in formulations.	Benzyl alcohol, phenol, thiomersal, butyl paraben, etc.	(Chaudhari SP & Patil PS, 2012)
Antioxidants	Delays or inhibit the oxidation of the drug molecules.	Sodium bisulphate, ascorbic acid, thiourea, Butyl Hydroxy Toluene (BHT), tocopherols, etc.	(Chaudhari SP & Patil PS, 2012)
Wetting agent	Lowers the surface tension of water.	Lecithins, Spans, Tween 80, Sodium Lauryl Sulphate (SLS), etc.	(Liberman HA *et al*,)
Thickening agents	Increases the viscosity of a liquid.	Microcrystalline cellulose, hydroxyethyl cellulose, methyl cellulose etc.	(Chaudhari SP & Patil PS, 2012)
Humectants	Minimizes the water loss thus control water content.	Glycerol, polyethylene glycol, propylene glycols, etc.	(Pockle RD *et al.*, 2023)

administration, dosage form, type of active ingredient and local regulatory requirements also influence excipient choosing. For instance, the Japanese Pharmaceutics Excipients Council (JPEC) in Japan assembles excipients in approved products; the FDA in the US offers a searchable list of approved inactive ingredients; and Health Canada in Canada publishes a list of acceptable non-medicinal agents (Rayaprolu BM *et al.*, 2018).

Additionally, a crucial factor in the selection of excipients is their functionality. The selection of excipients is dependent upon their capacity to carry out particular tasks within a reasonable range for a specific composition. It is interesting that an excipient may play different roles in different formulations or more than one role in a single formulation. As a result, excipients' suitability and functionality in a given medicinal product should be carefully considered. To further add to the complexity of their selection, excipients must be categorized. The International Pharmaceutical Excipient Council (IPEC) provides a framework for classifying

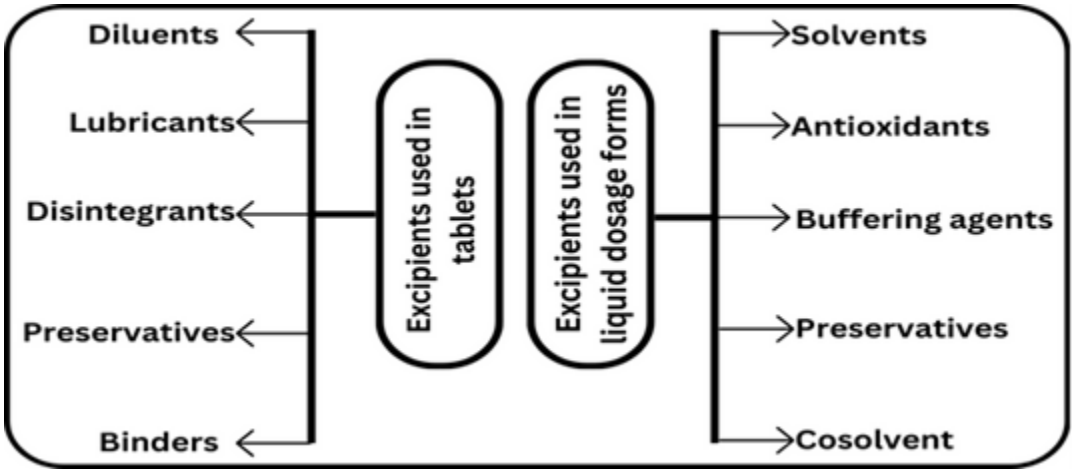

Figure 1: Excipients used in tablets and liquid dosage forms (Liberman HA *et al*,).

excipients so that their roles and functions can be better understood (Medi MB *et al*., 2014).

With their multifunctional nature and potential effects on the overall stability and cost of the medication, these categories help ensure that the appropriate excipients are selected for particular drug formulations. To sum up, the process of choosing excipients for pharmaceutical formulations is complex and requires a thorough evaluation of factors such as functionality, safety, compatibility, and regulatory compliance. Pharmaceutical scientists have more information to choose excipients for the creation of safe, efficient, and effective drug products by considering these variables and using the resources that are available for excipient classification (Medi MB *et al*., 2014).

Based on Safety and Toxicity

Concerning the development of safe and effective medications, the toxicity and safety of pharmaceutical excipients are crucial factors, as they are an essential component of drug formulations. A risk-based assessment that takes into account the possible risks and benefits of each excipient is part of the selection criteria for excipients based on safety and toxicity analysis. Excipients' potential toxicity, pharmacokinetics, and pharmacodynamics are all assessed as part of their safety evaluation. When assessing an excipient's risk/benefit ratio, it's important to consider both its intended use and the possibility of unforeseen consequences. After reviewing the safety and biopharmaceutical issues surrounding common excipients used in off-label pediatric formulations, recommendations were made to minimize the quantity of excipients used in a formulation. Pediatric patients may have an increased vulnerability to excipient-related adverse reactions because of their developing metabolism, elimination, absorption, and distribution pathways. Drugs designed for elderly patients are still frequently utilized off-label because few clinical studies have received regulatory approval. Excipients can be hazardous even if they are safe for adults because there is no evidence that they are safe for use in pediatric populations. Excipient toxicity is not related to dose, age, or route (Abrantes CG *et al*., 2016).

To summarize, the criteria for choosing excipients based on safety and toxicity involve a risk-based evaluation that takes into account the benefits as well as drawbacks of each excipient. The evaluation of excipient safety necessitates considering their intended purpose, possibility for unforeseen consequences, and the existing safety evidence. Excipients can be harmful due to several reasons, such as their chemical structure, impurities, and interactions with co-excipients or active pharmaceutical ingredients. Excipient safety is a crucial concern, and it is important to thoroughly assess how toxic they are (Belayneh A *et al*., 2020).

On the basis of compatibility with other active ingredients

A crucial part of developing pharmaceutical formulations involves selecting excipients that combine well with the active ingredient. A variety of methods, such as Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC), are typically used to assess compatibility. Because drug-excipient interactions are so complex, there are no universal standards for the evaluation methodology; however, more individual studies are reporting the use of different screening techniques. Studies on drug-excipient compatibility are conducted to evaluate possible interactions between the drug and excipients, which may affect the final drug product's performance, stability, and quality (Dave VS *et al*., 2015).

The International Council on Harmonisation (ICH) and the U.S. Food and Drug Administration (USFDA) have established the Q8 guidelines and the 21st-century Current Good Manufacturing Practices (cGMP) initiative, which both support the application of Quality by Design (QbD) principles in the drug development process, to ensure a logical selection of excipients. A thorough grasp of the physico-chemical characteristics and processes of

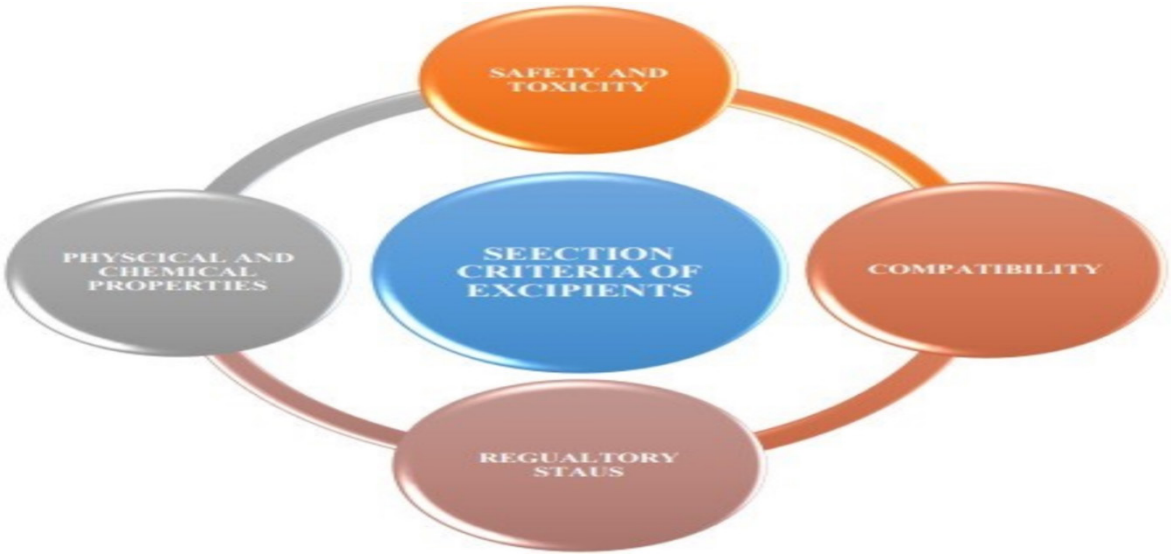

Figure 2: Selection criteria of excipients (Rayaprolu BM *et al*., 2018).

the drug and excipients is necessary to comprehend the direct interactions and potential impacts of these components on the final drug product. By identifying variations in heat flow values and changes in the endothermic or exothermic peaks, thermal techniques like DSC are especially helpful for evaluating incompatibilities. Regarding the drug's stability in both its pure form and at the prescribed dosage, these studies offer invaluable information. Although there are no set standards for carrying out drug-excipient compatibility studies, the pharmaceutical industry is aware of the importance of excipients for drug stability and the necessity of thorough evaluation. A key component of formulation development is choosing excipients that work harmoniously with the active ingredient. Using a variety of analytical techniques is also essential to ensure the effectiveness and quality of the finished drug products. When choosing excipients rationally, it's crucial to take compatibility assessment into account and apply QbD principles and thermal techniques (Omari D *et al*., 2023).

On the basis of Regulatory Status

Drug products require excipients as an essential ingredient, and the regulatory status of these ingredients determines how they are chosen. Excipients are reviewed by the FDA in relation to drug products when they are submitted as a Biological License Application (BLA), New Drug Application (NDA), or Investigational New Drug application (IND). Currently, there isn't a distinct review procedure in place for excipients. Stated differently, excipients are not reviewed by the FDA outside of the framework of an IND, NDA, or BLA. Both Japan and the European Union are in comparable situations. The FDA recognizes excipients found in drug products with its approval, and the industry views these excipients as permitted or allowed. Drug products require excipients as an essential ingredient, and the regulatory status of these ingredients determines how they are chosen. Excipients are reviewed by the FDA in relation to drug products when they are submitted as a Biological License Application (BLA), New Drug Application (NDA), or Investigational New Drug application (IND). Currently, there isn't a distinct review procedure in place for excipients. Stated differently, excipients are not reviewed by the FDA outside of the framework of an IND, NDA, or BLA. Both Japan and the European Union are in comparable situations (Yu YB *et al*., 2021).

Excipients are not approved or licensed on their own; instead, they are evaluated in conjunction with drug products. Rather, excipients found in pharmaceuticals with FDA approval are considered to be approved by the FDA. Flavoring agents undergo independent evaluation by FEMA. On September 7, 2021, the programme was implemented voluntarily, and the FDA urged excipient manufacturers to submit applications for FDA assessment of novel excipients prior to their duration of exposure or mode of administration.

Excipients are selected according to their efficacy, safety, and intended use. The European Medicines Agency (EMA), the FDA, and other regulatory bodies set the regulatory status of excipients, which forms the basis of the selection criteria. Excipients have different regulatory statuses in various countries and regions. For instance, in December 2017, the co-review procedure for excipients was enacted in China. All domestic and foreign manufacturers and owners of pharmaceutical excipients are required to submit their dossiers to the CDE in accordance with CFDA announcement No. 146.

The excipients' intended use influences the selection criteria as well. The Active Pharmaceutical Ingredient (API) compatibility, stability, and capacity to improve drug delivery are the three main factors considered when choosing excipients. Excipients are chosen in accordance with their efficacy and safety. Excipients need to be safe for ingestion by humans and shouldn't affect the drug product's therapeutic effect.

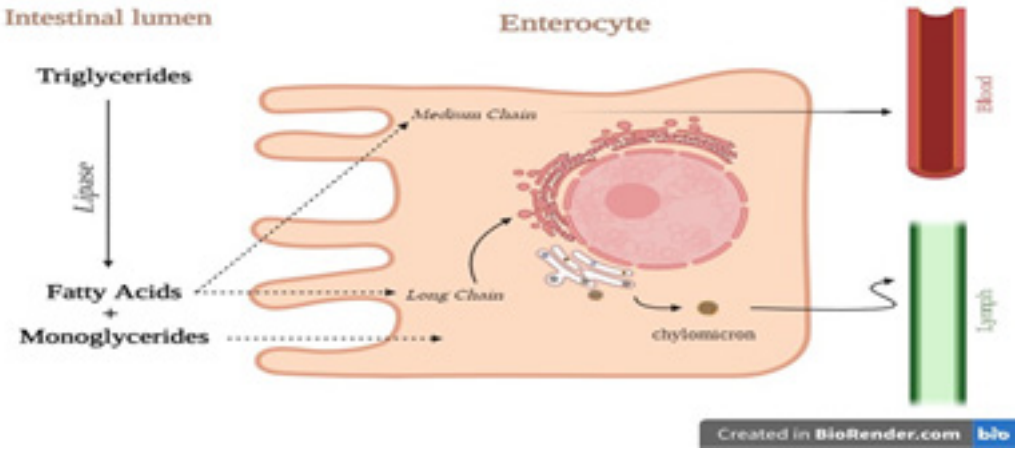

Figure 3: Lipid-based excipients facilitating drug absorption.

To sum up, the criteria used to select excipients are determined by their intended use, safety, and efficacy. Excipients are regulated differently in each country and area, and their status is assessed when they are used in pharmaceutical products. The FDA recognizes excipients found in drug products that have received FDA approval, and the industry views these excipients as permitted or allowed. On September 7, 2021, the FDA announced the opening of a voluntary Novel Excipient Review Pilot Program (Pilot Program), asking excipient manufacturers to submit proposals for FDA review of novel excipients before their length of exposure or mode of administration (Yu YB *et al.*, 2021; Saito J *et al.*, 2022).

On the basis of Physical and Chemical Properties

Excipients are typically regarded as inert additives added to drug formulation to aid in delivery or absorption, product differentiation, enhance appearance, or preservation of quality. Excipients are chosen according to their chemical and physical characteristics, which have an impact on the end product's efficacy, safety, and quality. Particle size, shape, density, and flowability are examples of physical characteristics that can impact the way an excipient processes and performs as well as the end product. Chemical properties such as solubility, stability, and reactivity can have an impact on the stability and compatibility of an excipient with an Active Pharmaceutical Ingredient (API).

High-resolution analytical methods on the molecular, particulate, and bulk levels can be used to assess the quality and functionality of excipients. Pharmacological excipients were categorized by the International Pharmaceutical Excipient Council (IPEC) according to their regulatory status and track record of human use. The category of excipients known as "new chemical excipients" can be further separated into "modified excipients" and "new chemical entities" that are incorporated into pharmaceutical products for the first time. The latter category may contain excipients that are already well-known. More advanced excipients are required to impart specific properties into the finished product as innovative drug delivery systems continue to advance (Felton LA, 2005; Pifferi G *et al.*, 1999).

Excipients with more than one purpose, such as a filler substance that is directly compressible and can also serve as a disintegrant or binder, are referred to as multifunctional excipients. A single excipient that serves multiple purposes, such as improving flow, acting as a disintegrant, and concurrently permitting a larger drug loading in the dosage form, is referred to as a high-functionality excipient.

Excipients can cause disruptions to the quality or efficacy of a drug by reacting chemically or physically with an active ingredient. Every incompatibility has the potential to manifest itself either overtly or covertly, and destabilization scenarios are real and should be looked into.

Excipients are selected depending on their chemical and physical characteristics, which have an impact on the end product's efficacy, safety, and quality. High-resolution analytical techniques can be used to characterize the molecular, particulate, and bulk levels of an excipient's quality and functionality. Pharmaceutical excipients were categorized by the International Pharmaceutical Excipient Council (IPEC) according to their regulatory status and history of human use. Excipients with high and multifunctionality can, respectively, carry out several tasks and offer extra functions. A detailed understanding of the chemical and physical properties of excipients, as well as any related impurities or residues, and how they may interact with other materials or with one another, can alert the pharmaceutical technologist to potential undesirable consequences (Felton LA, 2005; Pifferi G *et al.*, 1999).

INTERACTIONS

The quality or efficacy of the medication may be harmed by excipients' tendency to interact chemically or physically with the active ingredient. Drug molecules may adsorb to the surface of the excipient as part of these interactions, which may have an effect on absorption and particle size. The rate of dissolution and

bioavailability can also be impacted by finely divided excipients adhering to active components. Drug-excipient interactions can affect a number of physicochemical and physiological processes, which in turn might affect drug absorption. For example, a drug's action in the body may be altered by complexation agents interacting with the drug to produce a complex. Stabilizers may also influence the drug's recrystallization by lowering the dispersed drug's molecular mobility. These are only a few instances of how excipients might change a drug's efficacy and behavior. To ensure drug stability and bioavailability, it is crucial to comprehend the workings and implications of interactions between the drug and the excipient. Drug-excipient interactions of various kinds, as well as potential molecular explanations for these interactions, might result in incompatibilities that change the medication's intended characteristics. Pharmaceutical technologists need to know this information in order to foresee and minimize unfavorable developments in medication formulation (Rao VA *et al.*, 2020).

An important field of research is the relationship between pre-systemic medication metabolism and routinely used excipients. It has been discovered that excipients such fatty acids, solvents, polymers, and surfactants affect the expression of cytochrome P450 enzymes, which can change the rate of drug metabolism and bioavailability. When designing dosage forms, it is crucial to take the excipient's type, concentration, and other associated variables into account since they can have a substantial impact on the drug's metabolism (Patel R *et al.*, 2020).

In conclusion, complex interactions between excipients and drugs can have a big impact on the efficacy, performance, and quality of treatments. For the purpose of creating safe and effective medication formulations, it is imperative to comprehend these interactions. The numerous ways that excipients can affect drug behavior are still being investigated by researchers and pharmaceutical technologists in an effort to maximize drug stability, bioavailability, and overall therapeutic results (Rao VA *et al.*, 2020).

Drug-Excipients Interactions

Drug-excipient interactions are an important part of drug formulation because excipients aren't just inert additives; they can interact chemically or physically with the active ingredient, which could affect the drug's efficacy and quality. These interactions may have an impact on the stability and bioavailability of drugs and may occur through a variety of mechanisms, including adsorption, complexation, or incompatibilities. For example, drug molecules may adsorb onto the surface of excipients, influencing drug absorption and particle size, or complexing agents may interact with a drug to form a complex, affecting the drug's behavior. Furthermore, depending on variables like the therapeutic window, the site of absorption, and rate-limiting factors in drug absorption, the degree to which these interactions impact drug bioavailability varies (Rao VA *et al.*, 2020).

Common excipient categories, such as buffering agents, surfactants, lyoprotectants, and tonicity agents, were identified through a thorough analysis of excipients utilized in pharmaceutical products derived from biotechnology. This survey offers important information on the frequency of excipients in various drug classes and how they interact with different formulation parameters like pH, dosage form, and administration route.

Studies on the compatibility of excipients are carried out to forecast possible physicochemical incompatibilities of the drug in its ultimate dosage form. The purpose of these studies is to identify interactions that might impact the dosage form's stability, chemical, physical, and bioavailability. A crucial factor in the selection of pharmaceutical excipients is their safety (Vranić E, 2004). New excipients for use in drug or biological product formulations must adhere to safety profile development guidelines. These guidelines offer strategies for safety evaluations as well as recommended excipient toxicity testing for various pharmaceutical types. An effective tablet formulation should consider a number of factors when selecting its excipients, such as the target formulation, the manufacturing process, the properties of the Active Pharmaceutical Ingredient (API), and any potential effects on the formulation. The selection process involves several crucial factors, including excipient quality, functionality, and safety. In order to determine possible interactions that might affect the effectiveness and caliber of pharmaceutical formulations, drug-excipient compatibility studies are crucial. Pre-formulation studies are an important part of drug development, focusing on the interactions between drugs and excipients and their effects on stability, bioavailability, chemistry, and physical properties.

In conclusion, interactions between drugs and excipients are a complicated and important part of pharmaceutical formulation. For the development of safe and effective pharmaceutical products, it is crucial to comprehend the nature of these interactions, carry out compatibility studies, and ensure the quality and safety of excipients (Abrantes CG *et al.*, 2016).

Excipient-Excipient Interactions

Excipient-excipient interactions are important to understand in order to predict and prevent unfavorable developments in drug formulations. Excipient interactions have been found to have an impact on drug stability, bioavailability, and drug metabolism. For instance, excipients have been shown to alter drug bioavailability through their effects on cytochrome P450 enzyme expression. Excipients that have been found to influence drug metabolism include solvents, polymers, fatty acids, and surfactants. Excipient type, concentration, and other factors have been found to have an impact on the inhibition of CYP450 enzymes, emphasizing the significance of taking excipient effects into account when designing dosage form (Rao VA *et al.*, 2020).

Ensuring the safety, efficacy, and quality of the final product throughout the manufacturing of pharmaceutical formulations requires careful consideration of potential interactions between excipients. Comprehending the behavior of the excipients individually and collectively in the formulation requires an extensive understanding of their physical and chemical characteristics. Pharmaceutical technicians can maximize the efficacy and stability of a medicine by determining and evaluating excipient interactions (Patel R *et al.*, 2020).

To summarise, interactions between excipients can have noteworthy consequences for drug formulations, impacting elements like drug stability, bioavailability, and physicochemical results. For the purpose of minimizing potential side effects and designing pharmaceutical formulations logically, it is imperative to comprehend these interactions. Numerous studies have demonstrated how crucial it is to take excipient effects on drug metabolism into account when making formulation decisions, as well as how thorough understanding of excipient behavior is necessary.

Co-processed Excipients

Co-processed excipients are mixtures of two or more separate excipients that are physically combined without undergoing a substantial chemical alteration. In the pharmaceutical industry, they are widely used to simplify formulation development, improve product performance, and improve drug processability. These excipients are made to require the fewest possible ingredients and processing steps, which speeds up development, lowers manufacturing complexity, and streamlines processing. They may have to do with the manufacturing of drug products, *in vitro* or *in vivo* drug performance, or both. They can enhance functionality over straightforward physical mixtures (Serrano-Mora LE *et al.*, 2021).

Co-processed excipients perform more effectively in terms of flowability, particle size distribution, blending behavior, compressibility, storage stability, and batch-to-batch consistency. They may also result in fewer manufacturing expenses, quicker drug development, reduced time to market, and easier formulation development. Co-processed excipients can also cut down on the number of excipients required to attain good product performance, which will shorten the time needed to develop new drug products and simplify their manufacturing. Co-processed excipient development entails selecting the necessary excipients, figuring out their ideal relative proportions, selecting the best co-processing method, and optimizing a number of process variables. The majority of co-processed excipients consist of a filler and either a binder or a glidant, or a binder and a glidant and a filler. The development of novel co-processed excipients has been made possible by the availability of nanotechnology. It has been demonstrated that using co-processed excipients results in more patient-friendly formulations, less need for damaged tablet inspection, and improved product robustness. Additionally, by increasing solubility, bioavailability, stability, and overall drug performance, these excipients may help. In conclusion, co-processed excipients are a significant advancement in the pharmaceutical sector that provide many advantages such as simplified manufacturing, enhanced product performance, and streamlined formulation development. The application of these could result in lower costs and quicker drug discovery (Garg N *et al.*, 2013).

Excipients' effects on a drug's solubility and bioavailability

Drug-related dose forms and physiological features at the absorption site, as well as adjuvants that may impact oral bioavailability, can all have an impact on a drug's bioavailability. A complete understanding of the dependence on these interactions is required for the synthesis of complex molecules. Chemical excipients have the potential to increase emissions and waste associated with Active ingredients (APIs). Excipients that can be added to chemical formulations to aid in the dissolution of the chemicals or to provide variable degrees of improved water solubility by various ways include cyclodextrins, disintegrants, pH-modifying excipients, and surfactants (Sheikh M *et al.*, 2023).

Chemical and physical properties of drug formulations can be enhanced by the addition of excipients, which are inert substances. To increase the solubility of drugs that are poorly soluble, excipients play a critical role. A number of strategies, such as inclusion complexes, encapsulation, chemical modification of the API, physical modification, and dispersion, can be used to overcome solubility issues. For drugs with low solubility, excipients can help with numerous formulation techniques. For instance, for many years, drug particles have been maintained in Amorphous Solid Dispersions (ASDs) or the API has been solubilized in micellar structures, respectively, to improve the solubility of hydrophobic APIs. Polymers, surfactants, and lipids are the most often utilized excipients for improving solubility. Excipients with polymers are frequently utilized to improve solubility. When they combine with drugs, they can create inclusion complexes that improve the solubility of drug. Moreover, polymers can be utilized to create ASDs, which keep the medicine amorphous and inhibit crystallization, improving the drug's rate of solubility. Another family of excipients that can improve the solubility of poorly soluble drugs is surfactants. In aqueous solutions, they have the ability to create micelles that can solubilize the drug and boost its bioavailability. Additionally, lipids are employed as excipients to improve solubility. They have the ability to produce liposomes, which can encapsulate the medication and increase its bioavailability and solubility (Patel R *et al.*, 2020).

Naturally, lipid-based excipients facilitate drug absorption. Lipid-based formulations have the potential to increase API bioavailability through: promoting chylomicron production,

Table 3: Various Aspects of Consideration for Pharmaceutical Excipients.

Aspects	Summary	References
Importance of Excipients	Excipients are crucial components in drug formulations, making up 80-90% of the finished product. They enhance drug solubility, stability, bioavailability, and overall efficacy.	(Patel R *et al.*, 2020)
Functions of Excipients	Excipients play various roles such as improving stability, modulating bioavailability, preserving osmolarity and pH, enhancing patient acceptability, aiding in product identification, and ensuring safety and effectiveness.	(Li Z *et al.*, 2021)
Classification of Excipients	Excipients are classified based on their origin, function, and role in pharmaceutical formulations.	(Liberman HA *et al*,)
Selection Criteria	Ideal excipients should modulate bioavailability, prevent aggregation, and improve stability.	(Pockle RD et al., 2023)
Standardization of Excipients	Organizations like IPEC and guidelines like ICH Q8 support Quality by Design principles in excipient selection.	(Peng Soh JL *et al.*, 2015)
Emerging Trends	Co-processing for multifunctional excipients and green chemistry approaches are emerging trends in excipient technology.	(Saha S and Shahiwala AF, 2009)
Drug-Excipient Interactions	Drug-excipient interactions can impact drug stability, bioavailability, and efficacy, necessitating compatibility studies.	(Rao VA *et al.*, 2020)
Challenges and Future Directions	Risks in the excipient supply chain include sourcing issues, supply disruptions, and regulatory complexities. Strategies like dual-sourcing and regulatory frameworks like ICH Q12 are essential for maintaining a robust pharmaceutical supply chain.	(Available from)

which leads to increased drug absorption through the lymphatic channel and avoids the liver's first pass metabolism, and enhancing drug permeability through the intestinal epithelium. Medium chain lipids (C<12) permeate the enterocyte and enter blood arteries immediately. The lymphatic route facilitates the absorption of long unsaturated chain lipids (C18:1, C18:2).

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The drug's physicochemical characteristics and the desired formulation attributes influence the choice of excipient (Available from). To enhance a drug's solubility, for instance, salt production can frequently be explored if the molecule has an ionizable component. The stability of the drug may also be influenced by the application of excipients. Drug bioavailability can be affected by excipients that inhibit or increase the activity of cytochrome P450 enzymes, for instance, which can influence how quickly drugs are metabolized. As a result, it's critical to choose excipients carefully so that they don't interfere with the drug's stability or pharmacokinetics. The use of excipients is essential in improving the solubility of drugs that dissolve poorly. Excipients utilized most frequently for solubility enhancement are lipids, polymers, and surfactants. The pharmacological qualities and intended formulation features influence the excipient selection. The pharmacokinetics and stability of the drugs must be preserved while choosing excipients and therefore significant thought must be given to which ones work ideally (Available from).

Standardization of Excipients

To ensure the safety and effectiveness of pharmaceutical products, standardization of excipients is essential. A number of groups and programs, including the International Pharmaceutical Excipients Council (IPEC), have been set up to promote standardization across various guidelines for the production and application of pharmaceutical excipients. Several investigations have examined excipient variability, with a focus on how it affects the performance and processing of drug products. The source of the raw materials, the synthesis/manufacturing procedure, and the ideal concentration to be used in the finished product can all contribute to this variability.

The advancement of excipient standardization is greatly assisted by the International Pharmaceutical Excipients Council (IPEC). It seeks to promote the harmonization of various standards for the production and application of pharmaceutical excipients, eventually leading to the advancement of enhanced product quality and consumer safety. The organization also offers the pharmaceutical industry helpful guidelines and resources to ensure the quality and safety of excipients used in drug products (Peng Soh JL *et al.*, 2015).

The pharmaceutical industry has shown interest in excipient variability, with research concentrating on how it affects the functionality of dosage forms and the performance of drug products. This variation may affect a blend's homogeneity and content uniformity as well as the impact of various pharmaceutical

processes on the finished product. Pharmaceutical product performance and quality must be maintained, and this requires an understanding of and approach to excipient variability.

To further revolutionize drug formulation, the development of novel excipients has been a major area of focus in recent years. Reviewing novel excipients can help you better understand the types and uses of these cutting-edge excipients and how they can improve the functionality and performance of pharmaceutical formulations. The focus on new excipients highlights the ongoing efforts to enhance and standardize the components used in the creation of new drugs.

In conclusion, IPEC and other organizations are instrumental in promoting harmonized standards for excipients, which is a crucial component of pharmaceutical development. The variability of excipients has been studied in extensive detail, and the development of new excipients keeps pushing the boundaries of innovation in medication formulation. To ensure the effectiveness, safety, and quality of pharmaceutical products, it is crucial to comprehend and take care of these factors (Dureja H & Kumar D, 2013).

Excipient Stability Testing

Testing the stability of excipients is an important part of pharmaceutical formulation. A number of investigations have been carried out to assess the effects of excipients' chemical and physical instabilities on the finished product. The selection of excipients has a major impact on a number of formulation parameters, including shelf life, disintegration, and dissolution. To ensure the security and efficacy of oral solid dosage forms, excipient stability testing is crucial.

In excipient stability testing, the relationship between moisture and excipients and its effects on the stability of drugs that are sensitive to moisture are critical factors to take into account. The main goal of stability testing is to evaluate chemical deterioration in order to ensure that the product is safe for the duration of its shelf life. Chemical degradation is frequently studied through accelerated stability studies, and the results are frequently extrapolated for long-term storage. To assure product quality, pharmaceutical products, including directly compressed tablets, must also have their physical stability assessed in addition to their chemical stability (Darji MA *et al.*, 2018).

Planning and carrying out scientific studies to ascertain the stability of excipients is governed by guidelines provided by the International Pharmaceutical Excipients Council. These recommendations focus on the elements that should be taken into account when performing stability studies on excipients, such as the necessity of stability programs, the categorization of excipients according to stability, and the structure of stability studies. An excipient stability study's main goals are to demonstrate that the excipient will continue to fulfill the manufacturer's specifications, specify suitable storage settings, ascertain shelf life, and validate shelf-life claims.

Since forced degradation samples must include all potential degradation impurities, current regulatory requirements place a strong emphasis on the validation of stability indicating methods. Making sure the techniques utilized for stability testing are accurate and dependable is a crucial part of the validation process for pharmaceutical stability analysis (Chaudhari SP & Patil PS, 2012).

Excipient safety evaluation

To ensure the safety and efficacy of the finished product, pharmaceutical excipients are a necessary component of drug products, and their safety evaluation is critical. Excipient safety evaluation is a multifaceted process that takes into account a number of variables, such as the intended use, the mode of administration, and any possible interactions with active pharmaceutical ingredients and other excipients.

General status of pharmaceutical excipients

A review article states that one of the most important aspects of drug development is the safety of pharmaceutical excipients. According to the article, an excipient's efficacy, potential toxicity, and intended use should all be taken into consideration when calculating its risk/benefit ratio. In order to reduce the possibility of toxicity, the article also emphasizes how crucial it is to simplify the formulations as much as possible (Abrantes CG *et al.*, 2016).

Safety Assessment of new Pharmaceutical Excipients

An article offered a set of suggested guidelines for the evaluation of new pharmaceutical excipients' safety. The International Pharmaceutical Excipients Council's Safety Committee created the guidelines, which are based on the most up-to-date toxicological research available. The guidelines offer a method for establishing safe usage conditions for suggested pharmaceutical excipients that is grounded in science.

Toxicity testing of Excipients

Excipient toxicity testing is a crucial component of evaluating their safety; it should be carried out in compliance with good manufacturing practices, good distribution practices, good laboratory practices, and guiding principles in toxicology assessment. Genotoxicity and carcinogenicity studies should be included in the toxicity testing, in addition to acute, sub-acute, and chronic toxicity studies (Abrantes CG *et al.*, 2016).

Excipient Safety Evaluation in Parenteral Formulations

One of the most important parts of drug development is evaluating the excipient safety in parenteral formulations. Testing for pyrogenicity, sterility, and compatibility with other formulation

ingredients should be part of the safety assessment of excipients used in parenteral formulations (Abrantes CG *et al.*, 2016).

Excipient Safety Evaluation in Oral Formulations

The safety assessment of excipients used in oral formulations is one of the most significant parts of drug development. The Food and Drug Administration (FDA) of the United States provides guidelines for the safety assessment of prospective novel excipients intended for use in pharmaceutical products labelled for clinical use of longer than three months. This guideline describes testing procedures for drugs meant for short-, intermediate-, and long-term use as well as recommended excipient toxicity testing for pulmonary, injectable, and topical treatments. It emphasises how important it is to establish safe and appropriate limits for these compounds and do risk-benefit evaluations on proposed novel excipients.

Excipient Safety Evaluation in Topical Formulations

Ensuring the quality and safety of pharmaceutical products involves evaluating the safety of excipients used in topical formulations. A number of resources offer direction on this subject. The FDA's "Guidance for Industry" discusses testing procedures for drugs meant for short-, intermediate-, and long-term use as well as recommended excipient toxicity testing for topical treatments. It also covers suggested safety assessments for excipients that are suggested for use in over-the-counter and generic drug products.

Excipient Safety Evaluation in Ophthalmic Formulations

A critical component of drug development is the safety assessment of excipients used in ophthalmic formulations, especially given the sensitivity of ocular tissues. At the target site, ocular drug delivery systems need to maintain consistent, safe, and user-friendly concentrations. To satisfy the specifications of a certain medication formulation, excipients used in ophthalmic formulations go through particular processing and treatments. The necessity of evaluating the safety of ocular drug delivery formulations has become more pressing with the acceleration of the development of new drug candidates and innovative delivery methods for the treatment of ocular diseases. Furthermore, excipient safety and biopharmaceutical issues in off-label pediatric formulations have been examined, emphasizing the significance of using a risk-based assessment to support the use of excipients in pediatric formulations (Osterberg RE *et al.*, 2011).

Excipient Safety Evaluation in Inhalation Formulations

Excipient selection for inhalation formulations must be done carefully because there are few FDA-approved options and new excipients must undergo rigorous toxicity testing. The workload and uncertainty in the development of new drug products are increased by the absence of regulatory guidance on excipient safety evaluation. Certain non-clinical safety data can be replaced by human data for some excipients; however, it is preferable to use an excipient that has been shown to have been exposed to humans in the past under conditions pertinent to the intended use. Excipients can change the characteristics of drug particles and their aerodynamic behavior in inhalation formulations. However, there is a limited number of excipients that have been approved for use in pulmonary delivery, and using an unapproved excipient comes with additional work, expense, time, and the possibility of rejection by regulatory bodies (Osterberg RE *et al.*, 2011).

Nanotechnology based Excipients

Excipients based on nanotechnology are crucial for drug delivery systems because they provide benefits like enhanced solubility, stability, and targeted delivery. Polymers, targeting agents, coating agents, and lipids are examples of excipients for nanomedicines that are used to improve absorption or regulate the release of the drug substance. These excipients are necessary for stabilizing the finished pharmaceutical product and putting structures together. The categorization of excipients and pharmaceutical ingredients for nanomedicines, however, is up for debate, especially when it comes to regulatory review and product approval (Hemmrich E and McNeil S, 2023).

Drug delivery systems have been greatly improved by nanotechnology, making it possible to employ FDA-approved nanoparticle medications as adjuvants in combination cancer treatments. Because of their special qualities, drugs can be delivered to target sites with greater stability and specificity, increasing treatment efficacy. Additionally, nanotechnology has transformed imaging and diagnostic techniques, which has aided in the creation of precise and accurate drug delivery systems.

Drug delivery systems like nanoshells and nanobubbles are made from nanoparticles, which have special qualities that can be adjusted for different uses. While nanobubbles are formed at the nanoscale and can be stabilized at room temperature, offering opportunities for various medical applications, nanoshells, with a silica core and an outer layer of metal, are used for drug targeting. These nanostructures show how versatile and adaptable drug delivery systems based on nanotechnology can be (Mazayen ZM *et al.*, 2022).

Drug delivery systems based on nanotechnology have advanced significantly in the field of nanobiotechnology, with an emphasis on addressing the drawbacks of conventional delivery techniques. The delivery of medicinal drugs, biosensors, and tissue engineering applications may all be enhanced by nanoparticles because of their small size and special characteristics. It may be possible to get around current restrictions and improve the efficacy of drug delivery systems by using nanotechnology approaches in drug design (Serrano-Mora LE *et al.*, 2021).

Since they have special physical, electrical, magnetic, and optical properties, inorganic nanoparticles like gold, iron, and silica have been used in advanced nanoparticle designs for drug delivery. These engineered nanoparticles may increase the drugs' solubility and stability while also improving their transport and delivery properties. The goal of this field's continuing research and development is to produce precision nanoparticles for drug delivery applications that are both personalized and non-personalized (Yu YB *et al.*, 2021).

In conclusion, excipients and drug delivery systems based on nanotechnology have greatly advanced medicine and offered unique opportunities to raise the efficacy and accuracy of drug delivery. Because of their adaptability and variety of qualities, nanoparticles serve as helpful tools for the development of novel drug delivery systems that have the potential to overcome current constraints and improve patient outcomes (Sim S and Wong NK, 2021).

Natural and biodegradable excipients

Because of their sustainability, lower environmental impact, and biocompatibility, natural and biodegradable excipients have drawn a lot of attention in the pharmaceutical and biomedical industries. Numerous natural polymers, including hyaluronic acid, alginate, chitosan, and albumin, have been thoroughly studied for their potential in drug delivery systems. These polymers can be used in targeted and customized drug delivery systems because of their benefits, which include enhanced bioavailability, biodegradability, and biocompatibility. Natural polymers have also been investigated for application in cardiac tissue engineering, where their biodegradability and capacity to retain mechanical qualities are very advantageous. Chitosan is a naturally occurring polymer that is biocompatible, biodegradable, and nontoxic. Its exceptional film-forming capacity has made it a viable excipient for a range of pharmaceutical compositions. Natural polymers are also well-known for their sustainability, renewability, and abundance, all of which are crucial for the development of formulations that are ecologically friendly and green (Idrees H *et al.*, 2020).

Natural and biodegradable polymers have certain drawbacks in addition to their numerous advantages, like rapid disintegration and limited electrical conductivity. Despite these obstacles, scientists are still investigating and creating novel biodegradable polymers to improve traditional dosing systems and reduce the adverse impacts of pharmaceutical formulations on the environment. Excipients are essential in the production of dosage forms because they enhance the physicochemical characteristics of the product. The use of natural and biodegradable excipients is consistent with the pharmaceutical industry's increasing focus on ecologically conscious and sustainable operations (Pockle RD *et al.*, 2023).

The general sustainability of pharmaceutical formulations, tissue engineering, and drug delivery systems could all be significantly affected by the study and development of natural and biodegradable excipients, especially polymers. A dedication toward creating biomedical innovations while reducing environmental harm is evident in the continuous investigation of these materials (Patel R *et al.*, 2020).

Emerging Trends

Co-processing for Multifunctional Excipients

The method of coprocessing multifunctional excipients involves mixing two or more existing excipients at the subparticle level in order to produce a single, enhanced multifunctional excipient. Enhanced flow, compressibility, compactibility, and disintegration ability are a few examples of these qualities. As tablet manufacturing techniques have advanced, so has the need for excipients with enhanced capabilities, which has raised interest in co-processed excipients (Saha S and Shahiwala AF, 2009).

Coprocessing requires certain material characteristics, such as the physicochemical and mechanical properties of the excipients. There are several ways to accomplish coprocessing, and the excipients that are produced minimize the disadvantages of the individual components, providing significant advantages.

Research has demonstrated the benefits of utilizing natural ingredients in coprocessing and the possibility of creating customized, designer excipients to satisfy specific formulation requirements. Given the rising cost of creating new chemical entities and the preference for direct compaction processes, the development of high-functionality coprocessed excipients is viewed as a significant opportunity (Serrano-Mora LE *et al.*, 2021).

In addition, coprocessed excipient regulations must be taken into account. A current and emerging trend in excipient technology is the development of single multifunctional excipients rather than utilizing multiple separate excipients in formulations. In a nutshell coprocessing multifunctional excipients presents a viable way to meet the growing need in tablet manufacturing for excipients with better qualities. Subparticle-level excipient combinations have the potential to reduce the need for numerous separate excipients in formulations by producing high-functionality excipients with improved performance. Nonetheless, it's crucial to take regulatory concerns into account and make sure the co-processed excipients that are produced fulfill the precise functionality needs of the intended applications (Garg N *et al.*, 2013).

Excipient innovation for personalized medicine

A key factor in the advancement of personalized medicine is excipient innovation, especially when it comes to customized

pharmaceutical products and Personalized Drug Delivery Systems (PDDS). Drug formulations can be specific to each patient's unique needs by incorporating excipients, which are inactive ingredients, according to variables like age, sex, and genetic composition. This strategy may increase medication efficacy, lessen adverse effects, and improve patient outcomes. Moreover, excipient integration in personalized medicine may result in financial savings for insurers, healthcare providers, and patients. As the field of personalized medicine develops, the use of excipients is probably going to become more and more crucial for improving patient care.

The potential of 3D printing technology in the pharmaceutical industry has been suggested by recent advancements in personalized medicines that are 3D printed. Complex formulations can be created with 3D printing using straightforward methods, and they can be customized to meet each patient's unique needs. This technology can create precisely dosed medications and patient-tailored drug delivery systems, which could completely transform the pharmaceutical industry, especially in the context of personalized medicine. For widespread adoption, however, a number of technical, quality control, and regulatory issues still need to be resolved before 3D-printed personalized medications are practical (Omari D *et al.*, 2023).

The treatment of chronic diseases and the delivery of multiple drug doses customized for individual patients are made more difficult by the mass production-based structure of conventional pharmaceutical manufacturing today. As a crucial component of personalized medicine, Personalized Drug Delivery Systems (PDDS) aim to tailor the dosage form and drug release kinetics to each patient's specific requirements (Peng Soh JL *et al.*, 2015).

Bridging the gap between traditional pharmaceutical production and the demands of personalized medicine requires the integration of PDDS into digital health and the application of advanced manufacturing techniques. The role of excipients in customizing drugs for individual patients is becoming more widely acknowledged in the context of personalized medicine. Excipients can be modified to allow for the targeting specific tissues or cells, increasing drug efficacy and lowering side effects. They can also be used to improve the stability, safety, and efficacy of drug formulations. Everyone involved could potentially save cost if this customized approach to drug products can lower the quantity needed and increase the effectiveness of drug therapy (Vaz VM and Kumar L, 2021).

Excipient innovation has enormous potential to advance personalized medicine, especially in the areas of 3D printing and customized drug delivery systems. Excipients can help to increase drug efficacy, decrease side effects, and save costs by tailoring drug formulations and drug delivery methods to each patient's specific needs. To be widely adopted, these innovations in personalized medicine still face a number of technical and regulatory obstacles that must be overcome in order to be put into practice. The integration of excipients and advanced manufacturing techniques is anticipated to become more crucial as the field of personalized medicine develops in terms of enhancing patient care and treatment results (Vaz VM and Kumar L, 2021).

Advances in taste-masking technologies

In particular, taste-masking technologies are essential for improving the palatability of drugs taken orally for elderly and pediatric patients. Various techniques, such as physical methods involving the use of sweeteners, microencapsulation, and the effervescent base in drug formulations, are used to mask the unpleasant taste of drugs. Furthermore, powders, chewable tablets, and liquid suspensions have had their tastes masked by specialized methods like microemulsion technology. Many taste-masking techniques have been developed in response to the need for better palatability, demonstrating the significance of this parameter in ensuring patient compliance and preference (Sohi H *et al.*, 2004).

The basis of taste-masking technologies is the variation in taste thresholds and the use of different techniques to select the masking technology that best suits the Active Pharmaceutical Ingredients (API) characteristics. These technologies solve a major formulation challenge, especially for pediatric patients, by enabling the oral administration of bitter drugs with a tolerable degree of palatability. Since it is commonly known that unpleasant tastes can have a substantial negative influence on patient acceptance, particularly in younger patients, taste-masking technologies are an important area of focus for pharmaceutical development (Sheikh M *et al.*, 2023).

Taste-masking technologies refer to a range of techniques and strategies intended to mask the disagreeable taste of pharmaceuticals, thereby improving patient acceptance and adherence. The significance of taste-masking technologies in pharmaceutical formulation and the need to evaluate their efficacy to ensure the development of palatable and effective drug products are highlighted by the ongoing advancements in this field (Sohi H *et al.*, 2004).

Green chemistry approaches in Excipient Synthesis

Green chemistry techniques in excipient synthesis use non-toxic and sustainable solvents, raw materials, and reaction conditions in an effort to lessen the process's negative environmental effects. Natural products have been incorporated into topical green formulations as excipients. A review of using arginine as a building block to create environmentally friendly excipients has been conducted. The foundation of green chemistry, which aims to promote the use of environmentally friendly alternative reaction conditions and discourage the use of dangerous chemicals, is the 12 Principles of Green Chemistry. Green chemistry principles have been utilized in the synthesis of bio-based surfactants,

including sucrose esters and alkyl polyglucosides. The synthesis of pharmacologically active compounds can be complex, requiring multiple steps and harsh reaction conditions. This makes the synthesis of excipients using green chemistry approaches difficult.

In order to facilitate the sharing of best practices and knowledge, cooperation between industry, regulatory agencies, and researchers is required to fully apply green chemistry principles in excipient synthesis. Accurate control, selectivity, and resource efficiency can be made possible by continuous flow technologies, biocatalysts, and AI-driven methods. It is also necessary to have a deeper understanding of how the process affects the impurity profiles and products. Green and sustainable science is actively promoted in the pharmaceutical industry by groups like Merck (Rose HB *et al*., 2022).

Characterization of Excipients

The compatibility of excipients with Active Pharmaceutical Ingredients (APIs) is determined through compatibility studies. The physical and chemical interactions between excipients and APIs are discussed in these studies. To identify drug-excipient interactions and optimize drug formulation, spectroscopic and thermal analysis techniques like FTIR, UV-vis, DSC, and TGA are crucial (Bugay DE, 2001).

An important component of drug development is the physical characterization of pharmaceutical solids. Characterizing excipients is essential to ensuring the final product's quality, safety, and efficacy because they are an essential component of drug formulation. Characterizing excipients is a common use for spectroscopic methods like Ultraviolet-visible (UV-vis) and Fourier-Transform Infrared (FTIR) spectroscopy. The functional groups, chemical makeup, and purity of the excipients are all disclosed by these procedures (Patel R *et al*., 2020).

The thermal behavior of excipients is investigated using thermal analysis methods such as Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC). These methods yield data regarding the excipients' melting point, glass transition temperature, and thermal stability. The optimization of the drug formulation and the choice of excipients depend on this information (Pockle RD *et al*., 2023).

To ascertain the particle size distribution of excipients, particle size analysis methods like laser diffraction and microscopy are employed. The excipients' surface area, shape, and particle size are all disclosed by these methods. This information is essential for developing drug delivery systems and optimizing drug formulation (Belayneh A *et al*., 2020).

Excipients' flow properties are ascertained through rheological studies. These investigations offer details regarding the excipients' viscosity, elasticity, and plasticity. The development of drug delivery systems like gels, emulsions, and suspensions requires this knowledge (Felton LA, 2005).

Determining the surface area and pore size distribution of excipients is performed through measurements of porosity and surface area. The surface area that can be used for drug adsorption and the distribution of pore sizes that influence drug release are indicated by these measurements. Drug delivery systems like porous matrices and sustained-release formulations require this information to be developed (Darji MA *et al*., 2018).

Challenges and Future Directions

The manufacturing and distribution of safe and effective drugs are ensured by the intricate and strictly regulated pharmaceutical supply chain. It calls for meticulous care to detail, stringent quality assurance, and a steadfast dedication to the security and welfare of the patient. Every stage of the process is linked to the others, acting as an essential link in the chain, from sourcing raw materials to manufacturing, packaging, distribution, and final dispensing.

Specific risks pertaining to quality, regulatory compliance, and overall supply chain resilience are associated with the excipient supply chain. These risks include the requirement to assess and qualify both new and existing suppliers, as well as the interaction of performance, quality, testing, and compliance. Modern technologies, international cooperation between regulators and industry, and stakeholder collaboration on a global scale are necessary for ensuring high-quality excipients (Saito J *et al*., 2022).

The process of developing new drugs can be impacted by the sourcing of essential excipients, and supply chain disruptions can have serious repercussions. Critical excipient supply chains should be evaluated, and dual-sourcing tactics should be taken into account to reduce the risk of disruptions caused by things like shortages of raw materials, regulatory issues, and manufacturing difficulties (Rayaprolu BM *et al*., 2018).

Maintaining a robust pharmaceutical supply chain that can serve patients worldwide depends on the raw material regulatory environment. A consistent and flexible regulatory framework must be established due to a lack of resources and the complexity of regulations. Using guidelines such as ICH Q12 can help streamline the number of post approval submissions and make the supply chain more agile (Dave VS *et al*., 2015).

Pharmaceutical businesses must deal with issues related to regulatory compliance, supplier risk management, and supply chain continuity. By implementing digital technology and radically rethinking the procurement process, the crisis has presented an opportunity to enhance procurement capabilities. However, because of fixed costs and the difficulty of decentralized site-level purchasing, pharmaceutical companies have been hesitant to drastically improve procurement (Available from).

CONCLUSION

Regulatory compliance, safety, toxicity, compatibility, and other important factors are highlighted in pharmaceutical excipients. In assessing the possible dangers and advantages of each excipient, especially in connection to safety and toxicity, the paper emphasizes the significance of a risk-based evaluation. The need to do extensive research on drug-excipient compatibility is also highlighted in order to guarantee the efficacy, stability, and quality of the finished pharmaceutical product. The article also addresses excipients' regulatory status and the procedures used by regulatory organizations like the FDA and the European Medicines Agency to evaluate them. The conclusion highlights the intricate process of selecting excipients and the need for thorough assessment to guarantee the effectiveness, safety, and conformity of pharmaceutical formulations with regulations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **IPEC:** International Pharmaceutical Excipient; Council; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **CFDA:** China Food and Drug Administration; **QbD:** Quality by Design; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared; **UV-vis:** Ultraviolet-visible; **TGA:** Thermogravimetric Analysis; **PDDS:** Personalized drug delivery systems; **BLA:** Biological license Application; **NDA:** New Drug Application; **IND:** Investigational New Drug Application.

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