Research Article

Drug-Excipient, In-Process, And Packaging Compatibility Studies In Pharmaceutical Development: A Comprehensive Review

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Abstract

Compatibility studies play a crucial role in pharmaceutical product development by identifying, quantifying, and predicting potential interactions and incompatibilities between components in a formulation. These interactions can lead to changes in the physical, chemical, or therapeutic properties of the dosage form, potentially affecting its stability, safety, and efficacy. The primary objective of compatibility studies is to select compatible excipients, determine stable storage conditions, and ensure the overall quality, safety, and efficacy of the final product. This review delves into the various types of incompatibilities, their causes, and potential remedies. It also provides detailed information on drug-excipient, in-process component, and finished product-packaging material compatibility studies, along with their respective protocols. Drug-excipient compatibility studies, in particular, are a critical phase in the pre-formulation stage of drug development. Thermal and non-thermal methods are employed to evaluate the suitability and compatibility of excipients for developing stable dosage forms.

Key words: Incompatibility, Compatibility study, Thermal method, Nonthermal method, Protocols.

1.Introduction

In pharmaceutical formulation, ensuring compatibility between active pharmaceutical ingredients and excipients is imperative. Because of different excipients employed in various dosage forms, such as tablets, capsules, oral liquids, injectables, inhalers, topical creams, gels, transdermal patches, and suppositories, necessitate meticulous consideration.[1,2] In the 21st century, adherence to USFDA's current Good Manufacturing Practice (cGMP) and ICH Q8 guidelines promotes the incorporation of Quality by Design (QbD) principles in drug development. These guidelines underscore the necessity for a comprehensive understanding of interactions among formulation components. Recent advancements in thermal and nonthermal analytical techniques contribute to enhanced efficiency in early-stage detection, monitoring, and prevention of incompatibilities during the drug development process.[3]

2. Incompatibility

Pharmaceutical incompatibility refers to undesirable changes in the physical, chemical, or therapeutic properties of a drug product due to interactions between the active pharmaceutical ingredient (API) and excipients, or between excipients themselves. These changes can have a detrimental impact on the safety, efficacy, appearance, and stability of the drug product.[3,4,5] Incompatibilities can occur at various stages of the drug product lifecycle, including compounding, formulation, manufacturing, packaging, dispensing, storage, and even during administration.[6]

3. Types Of Incompatibility

3.1. Physical incompatibility:

When two or more substances interact, they can produce changes in color, odor, taste, viscosity, and morphology, caused by insolubility, immiscibility, precipitation, and liquefaction.[6,7]

Table 1. Physical incompatibilities[6,8,9]

Types	Definition	Remedy

Insolubility	Inability of material to dissolve in a particular solvent system.	**Eg:** Corticosteroid injection Corticosteroid are difficult to wet with water. **Remedy:**Add sufficient quantity of wetting agent (polysorbate).
Immiscibility	When two ingredients are combined resulting in a non-homogenous product.	**Eg**:Castor oil emulsion Castor oil is immiscible in water due to high interfacial tension is produced in ingredients. **Remedy:**Add sufficient quantity of emulsifying agent (Gum acacia).
Liquification	On mixing of low melting solid substance together, the solid converts to liquid state.	**Eg:**Addition of menthol and camphor Liquifiable of mixed together. **Remedy:** Add absorbent powder like magnesium carbonate or kaolin.
Precipitation	In a solubilized drug may be precipitate in a solution, if a non-solvent is added to the solution.	**Eg:**Benzoin tincture Tincture benzoin compound contain resins. this change solvent system to form precipitate. **Remedy:**Addition of tincture with solvent on rapid stirringto yieldfine colloidal dispersion.

3.2. Chemical incompatibilities:

When two or more substances react with each other, they can undergo chemical changes that alter their properties. These changes can be characterized by various phenomena, including pH changes, oxidation-reduction reactions, acid-base hydrolysis, double decomposition, and complex formation.[6,7]

Table 2. Chemical incompatibilities[6,7,10]

Types	**Definition**	**Remedy**
Oxidation	The condition of loss of electron or gain of oxygen is termed as oxidation.	**Eg:**Ascorbic acid Oxidation occurs by free radical and molecular oxygen. **Remedy:** Antioxidant(butylated hydroxy anisole) Chelating agent (EDTA)
Hydrolysis	The chemical reaction in which water react with a compound and break its covalent bond.	**Eg:**Aspirin, Procaine Hydrolysis occurs by presence of ester and amide group. **Remedy:** Addition of buffers (Boric acid) Addition of complexing agent (caffeine)
Decarboxylation	When the bicarbonate group ingredients used in formulation, the carboxyl group is removed by chemical reaction.	**Eg:** Procaine, Sodium p-amino salicylic acid **Remedy:** Add suitable non-acidic vehicle Buffer is using to maintaining the PH for the stability of the drug ingredients. Maintain Suitable temperature.

Polymerisation	When a small repeating units (monomer) are bonded to form a long chain polymer.	**Eg:**Ampicillin, Ceflazidime, Adrenaline injection Adrenaline undergoes to produce black brown pigments. **Remedy:** Protect from light Use suitable solvents Maintenance of temperature Use proper buffers
Isomerisation	Interconversion of one stereochemical form into another form.	**Eg:** vitamin A, tetracycline **Remedy:** Use of vehicle Maintenance of temperature Protection from impurities

3.3. Therapeutic incompatibilities:

When two or more substances are combined, they can interact in ways that alter their therapeutic effects or intensity, leading to outcomes that differ from those intended for the patient.[6,7]

Table 3. Therapeutic incompatibilities[6,9]

Types	Definition	Remedy
Overdose	Patient health may convert a single dose in to an over dose.	The drugs should be given in the specific described form where in the drug produce maximum effect.
Underdose	A drug effect is either reduced or antagonist by another drug.	Dosing errors should be avoided.
Contraindicated drugs	Some drugs either alone or in combination are contraindication in particular diseased condition.	The drug contraindicated in patient with specific disease should not be used.
Error in dosage	It occurs writing or interpreting the prescription order and dispensing is overdose of the medication.	Prescriber recheck the prescription and correct the overdose.
Wrong dose	Drug having similar name and these are prescribed.	Pharmacist check prescription and find errors and clarified by physician.
Prescribing synergistic and antagonistic drug	Two drugs are prescribed together. Increase the activity of eachother is called synergistic. It decreases the activity of eachother is called antagonistic drug.	Prescription referred by prescriber make corrections.

Table 4. Examples of incompatibilities[1,11]

S.No	Excipient	API	Reason for incompatibilities
Physical incompatibility			
1.	**Binder:** Polyvinyl pyrrolidone (PVP)	Haloperidol, Atenolol, Ranitidine, Indomethacin, Ibuprofen, Ketoprofen, Sulfathiazole.	PVP interact with the drug to produce amorphous dispersion
2.	**Chelating agent:** Sodium edetate, Sodium	Hydralazine	The chelating agent interact with hydralazine to produce yellow

	bisulfite		coloration was
Chemical incompatibility			
3.	**Diluent:** Lactose	Acyclovir, Aceclofenac, Ketoprofen, Metformin, Amlodipine, Lisinopril, Fluconazol, Primaquine, Promethazine.	Lactose is reducing sugar that react with amino group containing API to produce chemical incompatibility (maillard reaction).
4.	**Anti-adherent, lubricant:** Magnesium stearate	Aspirin, Acyclovir, Glipizide, Glimepride, Erythromycin, Clopidogrel.	Magnesium stearate is reacts with aspirin to produce number of potential undesirable product such as salicylic acid, salicyl salicylic acid and acetyl salicylic acid.
Therapeutic incompatibility			
5.	**Coating agent:** Eudragit (RS100 and RL 100)	Diflunisal, Flurbiprofen piroxicam	Eudragit is interact with NSAID to produce therapeutic incompatibility (acidic nature and presence of ammonium group in Eudragit that affect drug release profile from solid dispersion).
6.	**Surfactant:** Sodium lauryl sulfate (SLS)	Chlorpropamide	Therapeutic incompatibility (low dissolution rate of API).

4. Stability Studies

Stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.[12]

4.1. Solid – State Stability Studies

Solid-state stability deal with physical stability (change in physical properties of drug and dosage forms) and thermodynamic stability (change due to temperature and pressure).[10] These solid-state reactions are much slower and more difficult to interpret than solution state reaction, due to reduce number of molecular contacts between the drug and excipient molecules. These studies are used to predict stable storage condition of solid dosage form.[4]

4.2. Solution State Stability Studies: [4]

Solution state stability is easier to detect as compared to solid-state stability. According to stability guidelines by FDA states that, following conditions be evaluated in studies on solutions or suspensions of bulk drug substances,

(1) High oxygen and nitrogen atmosphere
(2) Presence of added substance: chelating agent, stabilizers, etc.
(3) Acid or alkaline pH
(4) Effect of stress testing condition

4.3. Drug – Excipient Compatibility Studies: [3]

Objectives:

- Identify compatible excipients for a stable formulation.
- Determine stable storage conditions for the drug in solid or liquid form.
- Ensure final product quality, safety, and efficacy.
- Develop a final product that is stable and patient-acceptable.

Importance of Compatibility Studies:

✓ Compatibility studies can maximize the stability and bioavailability of the dosage form by identifying potential physical or chemical interactions between the drug and excipients beforehand.

- ✓ These studies help prevent unexpected problems arising from drug-excipient and excipient-excipient interactions. By identifying potential reactions early on, we can avoid issues during the final dosage form development process.
- ✓ Compatibility studies provide a list of suitable excipients for use in the final dosage form.
- ✓ Drug-excipient compatibility study (DECS) data is crucial for Investigational New Drug (IND) submissions.
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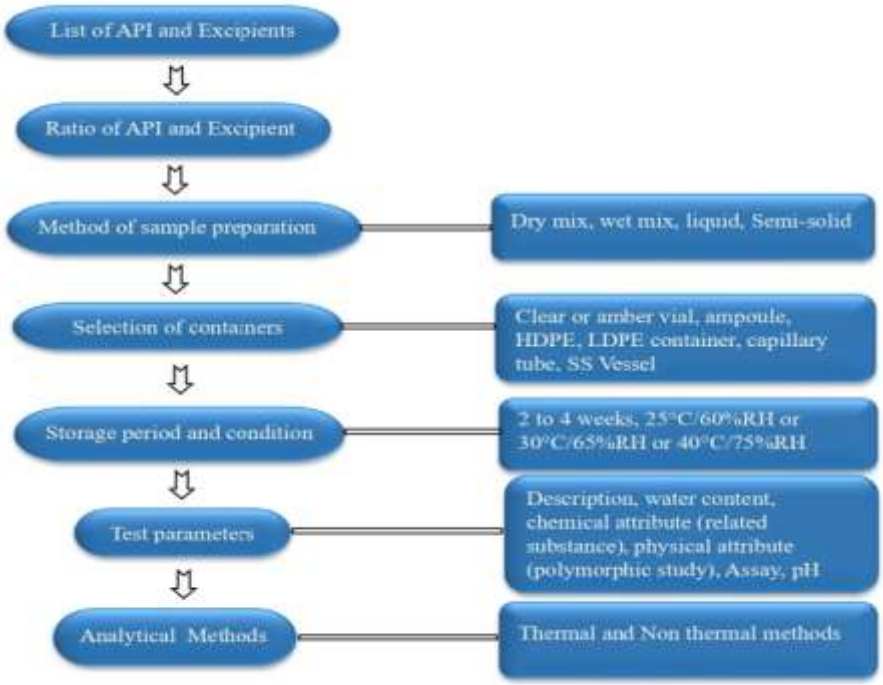
A universally accepted protocol for evaluating drug compatibility with other components remains elusive. Conventional compatibility testing methods, such as isothermal stress testing, necessitate both extensive sample preparation and prolonged storage periods to yield reliable results. To circumvent the lengthy storage conditions,thermal and nonthermal analytical techniques have emerged as promising tools for early excipient selection.[13,14]

4.3.1. Sample Preparation: [15,16,17]

Binary mixtures of API and selected excipients are prepared in a 1:1 (m/m) ratio by manual trituration in an agate mortar with pestle for 5 minutes. This ratio is chosen to maximize the lprobability of observing any interactions.

Figure 1. Compatibility study – A overview



4.3.2. Analytical Methods

Analytical methods for drug-excipient compatibility studies vary in their operating principles, the mechanical and thermal stress applied to the sample, analysis duration, sample size, sensitivity to minute changes, and the requirement for internal or external standards.[3,5]

4.3.3 Thermal Methods

Thermal method refers to a group of techniques in which a physical property of a substance and/or a reaction product is measured by using thermal energy. [18]

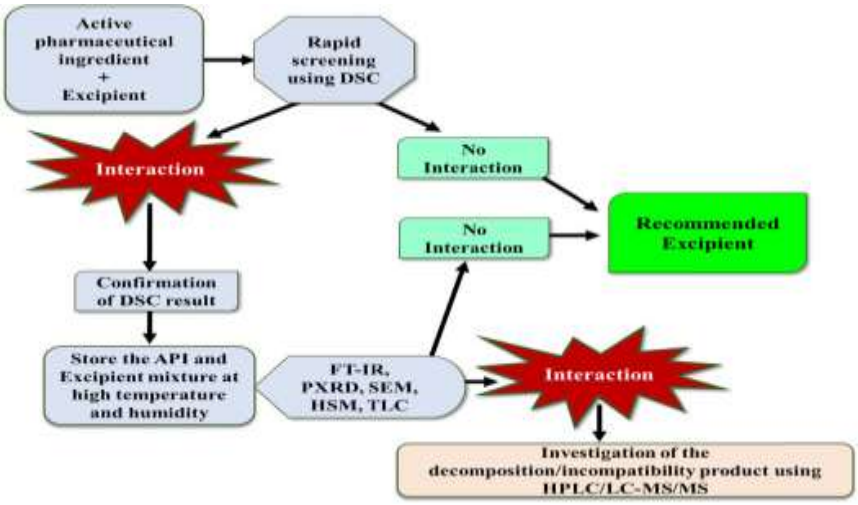
1) Differential Scanning Calorimetry (DSC):

It investigate and predict potential interactions between a drug and excipient by measuring the heat flow associated with transitions in the enthalpy of the sample. In this method, heat is either evolved or absorbed by the sample as it undergoes physical or chemical changes.[2,19]

- ✓ Samples were directly weighed in the DSC aluminium pan
- ✓ Keep temperature range is 25°C to 400°C under atmosphere of dry nitrogen
- ✓ During the process identically increase the temperature rate is 10°C per minute

✓ Observe thermal properties like melting point and enthalpy, peak shape, height, width etc. by comparing of samples thermogram[2,13,18]

Figure 2. Scheme to identify chemically compatible Excipients



2) Thermogravimetric Analysis (TGA):

TGA measure changes in sample weight as a function of time or temperature under a controlled atmosphere. Desolvation and Decomposition process are frequently monitored by this method.[20]

- ✓ Samples are directly weighed on the sample holding
- ✓ Keep the temperature range is 25 - 900ºC under atmosphere of dry nitrogen
- ✓ During the process identically increase the temperature rate is 10ºC per minute
- ✓ Changes in weights are recorded in different time intervals by comparing of thermogram[16,20]

3) Hot Stage Microscopy (HSM):

Hot stage microscopy is a fusion technique used for investigate physical and chemical incompatibilities like morphology, polymorphism, melting points, transition temperature and rate of transition at controlled heating rates.[20] HSM studies may prove helpful in avoiding the misinterpretation of the results obtained from DSC/TGA.[21]

- ✓ One milligram Sample is spread on the microscopic slide
- ✓ Slide placed on the microscopic hot stage
- ✓ Sample is heated at different rates under a controlled atmosphere
- ✓ The physical changes of sample are visually observed by to pass through the light from microscope[20,21]

4) Isothermal Microcalorimetry (IMC):

Isothermal microcalorimetry or Isothermal stress testing is used for to predict possible incompatibilities between API and excipients before deciding on a suitable dosage form.

- ✓ Binary mixture is weighed in the glass vial
- ✓ Mixture is mixed on a vortex mixer for 2 mins
- ✓ Samples are sealed by using a Teflon lined screwcap
- ✓ Then samples are stored in with or without moisture at high temperature to accelerate drug aging interaction with excipients
- ✓ End of the process the samples are visually observed and after the 1 month the samples are quantitatively analysed [18,22]

4.3.4 Nonthermal Method

1). Powder x-ray Diffraction (PXRD)

Powder X-ray diffraction (PXRD) is a powerful analytical technique used to identify the polymorphic nature, particularly the crystalline structure of materials. Each crystalline material produces a unique PXRD pattern, characterized by the intensity of diffracted X-rays plotted against a range of diffraction angles (2θ). Interactions between active pharmaceutical ingredients (APIs) and excipients that alter the crystalline form of the API are typically manifested as shifts, appearances, or disappearances in these peak intensities.[3]

2). Fourier Transform Infrared Spectroscopy (FTIR)

The excipient, active pharmaceutical ingredient (API), and their binary mixtures were subjected to FTIR analysis using a KBr disc method. The samples were maintained at room temperature and scanned within the wavenumber range of 400 to 4000 cm-1. The resulting spectra were compared to reference spectra to identify and characterize the components present.[22]

3). High Performance Liquid Chromatography (HPLC)

Its ability to separate and identify individual components in complex mixtures makes it ideal for evaluating potential interactions between drugs and excipients, ensuring the stability and efficacy of pharmaceutical formulations. In the drug-excipient compatibility studies, HPLC plays a crucial role in detecting and characterizing potential interactions that could compromise the stability or therapeutic activity of a drug product. By analyzing samples of the drug-excipient mixture before and after exposure to stress conditions, such as elevated temperature or humidity, HPLC can reveal changes in the drug's chemical structure or concentration, indicating a possible interaction.[23]

4). Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) is a powerful technique that provides high-resolution images of the surface of a sample, revealing its three-dimensional (3D) photography and revealing intricate details of its morphology. This technique is also valuable for identifying additives, impurities, and signs of degradation in materials. By employing a focused beam of electrons to interact with the sample, SEM can generate various signals that provide information about the sample's composition and structure. SEM is often used in conjunction with other thermal and spectroscopy techniques, such as differential scanning calorimetry (DSC), high-speed microscopy (HSM), and Fourier-transform infrared spectroscopy (FTIR), to gain a comprehensive understanding of the sample's properties and interactions.[5,24]

5). Thin Layer Chromatography (TLC)

In the drug- excipient mixtures, TLC can be employed to assess the purity of active pharmaceutical ingredients (APIs) and identify potential impurities or degradation products. The technique can also be used to monitor the progress of synthetic reactions involving APIs and optimize formulation parameters. Additionally, TLC can be used to compare the composition of different drug formulations and assess their stability over time.The detection of separated components on a TLC plate is typically achieved using visualizing agents, also known as spray reagents. These reagents interact with specific functional groups present in the sample components, causing them to appear as colored spots. The distance traveled by each component relative to the solvent front, known as the Rf value, serves as a unique identifier for that component.[2]

6). Solid State Nuclear Magnetic Resonance Spectroscopy (ss NMR)

Solid-state NMR spectroscopy (ssNMR) is a powerful tool for investigating drug-excipient interactions in the solid state. By measuring the chemical shifts of nuclei in the drug and excipient molecules, scientists can identify changes in electron density that indicate the formation of intermolecular bonds. Additionally, ssNMR can be used to directly measure the mobility of water molecules in the drug-excipient system, which can have a significant impact on the stability and efficacy of the drug product.[5]

4.4. In-Process Component Compatibility Studies: [25]

1.Filter Compatibility Study

The filter compatibility study aims to assess the interaction between the filter material and the sample stream, reducing the risk of structural failure during filtration. The purpose of this study was to determine the effect of stability on prolonged exposure of filter membrane to drug product

1. **Dynamic filtration:** Dynamic filtration involves continuously circulating the liquid through the filter membrane repeatedly. This method is more representative of actual filtration conditions and provides insights into the filter's performance under dynamic flow conditions.
2. **Static soak method:** The filter is immersed in the drug product solution for an extended period. This method is suitable for evaluating the adsorption capacity of the filter material under static conditions.

2. Silicone Tubing Compatibility Study

Silicone tubing's are commonly used as processing aid during filtration and filling operation for transfer of liquid in pharmaceutical manufacturing. They are known to absorb or interact with product and may lead to instability of product.The purpose of this study was to determine the effect of silicone tubing exposure on drug product characteristics..

Dynamic condition: Under the dynamic condition, the liquid sample will be continuously passed through the tubing at a controlled flow rate for a specified duration. This will enable the evaluation of the liquid's behavior under flow conditions, including its viscosity and flow characteristics.
Static condition: In the static condition, the liquid sample will be held stationary within the tubing for an extended period. This will allow for the observation of any changes in the liquid's properties over time, such as sedimentation or aggregation.

3.SS Vessel Compatibility Study
SS Vessels are commonly used in fabrication, filtration and filling of drug products. During this hold period the drug product may interact with SS 316 vessel and this may lead to incompatibility. The compatibility study with SS vessel is required to establish holding period

4.5. Finishing Product-Packaing Material Compatibility Study:
The packaging material, or container closure system (CCS), plays a crucial role in safeguarding the integrity of the finished drug product throughout its storage, distribution, and usage. During this period, it is imperative that the container and closure, along with any printing inks or label adhesives, maintain a state of chemical and physical inertness with the product. This is particularly important because the packaging material comes into direct contact with the drug product. If any interaction occurs, it could compromise the strength, quality, or purity of the product. The choice of an appropriate CCS hinges on several factors, including the route of administration, the class of drug product, its therapeutic range, the physical and chemical stability of the drug substance and product matrix, the packaging components themselves, and the anticipated storage and usage conditions. Plastic and elastomeric materials, in general, exhibit a higher potential for interaction with drug products compared to glass and stainless steel, which are considered inert due to their non-reactive nature. Therefore, selecting the most suitable CCS requires careful consideration of these factors to ensure the optimal protection and preservation of the drug product's integrity throughout its lifecycle.[7,26]

4.5.1. Mechanism of Container - Content Interaction: [26]
Migration of the product in to the container
1. **Adsorption:** the product interact with container on the surface
2. **Absorption:** the product penetrate into the container
3. **Permeation:** the product crossing the wall of the container - inside to outside

Migration of the container components in to the product
1. **Release :**The container component are release in to the product
2. **Permeation:** The foreign substance crossing the wall of the container - outside to inside (this aspect must be consider for semi-permeable material - eg: plastic bags)

1. Extractable study:[26,27,28]
Extractable are organic and inorganic chemicals released from packaging material when contact with extraction solvent (polar or non-polar) under extreme condition (temperature and time).

Experimental procedure
- ✓ The packaging material is filled by organic solvent in different polarity, PH and ionic strength.
- ✓ It is normally conducted at elevated temperature using extraction techniques such as less aggressive temperature, reflux, Soxhlet, sonication, accelerated solvent extractor, or extraction in a sealed container placed in oven or autoclave.
- ✓ In this condition presence of any possible extractables are released at regular time intervals.
- ✓ The resulting solution is analysed with advanced instruments to identify and quantify extractable substance.

2.Leachable study:[26-30]
Leachable are chemicals released into the drug product when contact with packaging materials or during manufacturing process under normal storage condition or acceleration storage condition.

Experimental procedure
- ✓ The packaging material is filled by drug product and placebo.
- ✓ Stored at normal and accelerated conditions.
- ✓ In case if any possible impurities present these are released.
- ✓ At regular time intervals the resulting solution is analysed.

5. Conclusion

Incompatibility affects the efficacy, safety, appearance and stability of pharmaceutical product. It occurs during in-vitro and in-vivo to form undesirable products. Pharmaceutical incompatibility is classified by three types including physical, chemical and therapeutic incompatibilities. Physical incompatibilities are occurs during of formulation, chemical incompatibilities are occurs during of storage period and therapeutic incompatibilities are occurs during after administration of dose. These Incompatibilities are predicted by compatibility studies and its provides clear understanding of any interactions between the formulation components.It assures the stability and bioavailability of the final dosage form.

The DECS is a type of stability studies, used for avoid the surprise problems before formulating final dosage form and to select compatible excipient. In the DECS the thermal and nonthermal methods are important one. The drug excipient binary mixtures are stored in different conditions and to analyse in different instruments like DSC, TGA, FTIR, etc,. The different inprocess-component compatibility studies are conducted in during of manufacturing process. Majorly to perform filter compatibility, silicone tube and SS vessel compatibility studies and to identify test parameters like description, assay, pH, etc., The packaging material are directly contact with finished product. The potential interaction is predicted by to conducting packaging-product compatibility study. Its help the selection of appropriate container closure system. This study conducted by performing of extractable and leachable test. This data is essential for Investigational New Drug (IND) submission. This review will be a very useful reference for future researchers about to development of new drug form and conduct compatibility studies.

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Author Contributions

P. Priya performed the literature search, collected and analyzed the relevant scientific publications, drafted the manuscript, and prepared the tables and figures. S. Radhakrishnan conceived the review topic, supervised the work, critically reviewed the manuscript, and approved the final version for publication. M. Surenthiran, A.N. Venkatesh, R. Sivanandhan, C. Kannan, R. Sambathkumar, and S. Giriprasath contributed to the literature review, scientific discussions, manuscript editing, critical revision, and interpretation of the published findings. All authors have read, reviewed, and approved the final manuscript and agree to be accountable for all aspects of the work.

Conflict of Interest

The authors declare that there are no financial, commercial, personal, or professional conflicts of interest that could have influenced the work reported in this manuscript. All authors have reviewed and approved the final version of the manuscript and agree with its submission for publication.

Data Availability Statement

This article is a comprehensive review based exclusively on previously published literature. No new datasets were generated or analyzed during the preparation of this manuscript. All information supporting the findings of this review is available within the article and through the references cited.

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