INVESTIGATING THE EFFECT OF SEGREGATION IN THE MANUFACTURING OF SOLID DOSAGE FORMS IN PHARMACEUTICAL INDUSTRIES IN NORTHERN INDIA

A Thesis Presented in Partial Fulfilment of The Requirements for the Degree In

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CANDIDATE DECLARATION

I hereby certify that the dissertation I have submitted for the master's degree in pharmaceutical business and technology, titled " **Investigating the effect of segregation in the manufacturing of solid dosage forms in pharmaceutical industries in Northern India** " is entirely original work of mine, and that the reference page contains an acknowledgement of all the resources I used in the research process.

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ABSTRACT

Tablets are the most often used solid oral dose form due to their high patient compliance, stability, simplicity of handling, and convenience of transportation. Tableting technology has come a long way over the years. Due to issues with segregation, content homogeneity, and physical stability, mixing and formulating solid dosage forms can be extremely difficult. When producing solid dosage drug products, these variables must be carefully controlled. A homogeneous and segregation-free dosage formulation must be developed, which requires careful consideration of the excipients used at each stage of the formulation and process development process. A wide range of equipment has been developed to make it easier to combine excipients with solid dose pharmaceuticals. There have been reports of several novel formulation procedures in addition to traditional methods including direct compression, wet granulation, and dry granulation. With the goal of establishing content homogeneity during the mixing and formulation of solid dosage medications, these technical innovations have enhanced the manufacture and quality of solid dose medicinal products.

This study aims to thoroughly examine the segregation techniques currently used by pharmaceutical companies in Northern India, assessing how well they comply with industry best practices and regulatory standards. By addressing and taking into consideration the factors, challenges, and limitations in the business, the author of this study examined the degree of the concerns generated by segregation in the Indian pharmaceutical sector in the context of a thorough literature analysis. The author's expertise of this subject was enhanced by earlier publications, which helped her collect the primary data for her research study. Through an investigation of challenges encountered by manufacturers during the implementation of effective segregation methods, the study aims to offer pragmatic perspectives and suggest suggestions for enhancing production procedures.

An online questionnaire survey consisting of fourteen questions was distributed to a group of pharmaceutical experts employed in various pharmaceutical organizations around Northern India in order to collect data for this study. This study highlights the various strategies incorporated in pharmaceutical manufacturing. With insights that can help with product quality, regulatory compliance, and eventually patient access to safe and effective pharmaceuticals, the expected results will have a major impact on the pharmaceutical sector in Northern India. At present, the Indian pharmaceutical industry is dedicated to enhancing its

production processes through the use of measures aimed at reducing segregation. With time pharmaceutical industries have ventured to adapt innovative ideas for a better future ahead.

Keywords: tablet manufacturing, content uniformity, blend homogeneity, blend segregation, and powder segregation.

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ABBREVIATION:

API: Active Pharmaceutical Ingredient

CU: Content Uniformity

DCGI: Drugs Controller General of India

DEM: Discrete Element Modelling

GMP: Good Manufacturing Practices

IBC: Intermediate Bulk Container

NIR: Near Infrared Spectroscopy

PAT: Process Analytical Technology

PDG: Pneumatic Dry Granulation

QbD: Quality By Design

RPM: Revolution Per Minute

RSD: Relative Standard Deviation

1. INTRODUCTION

1.1. BACKGROUND:

The pharmaceutical industries, which produces a wide range of necessary pharmaceuticals to address diverse medical ailments, plays a crucial role in the healthcare system. Making solid dosage forms, such tablets and capsules, is a critical step in the process of producing pharmaceutical products that are safe, effective, and cost-effective. The phenomena of powder segregation is one of the main challenges in this method of processing.

A pharmaceutical formulation that contains distinct components distributed unevenly is referred to as "powder segregation," and it can result in differences in the drug's quality and content. The final dosage forms' safety, efficacy, and overall quality may all be significantly impacted by this issue. In Northern India, where a significant amount of the country's pharmaceutical production occurs, the effects of powder segregation necessitate careful consideration and research. (Baxter and Prescott, 2009)

Powder segregation may be influenced by a number of complex processes used in the production of solid dosage forms, including coating, granulation, compression, and mixing. It is essential to comprehend the underlying causes, prevalence, and effects of powder segregation if the pharmaceutical industry is to continue manufacturing high-quality therapeutics.

The purpose of this study is to fill in the information gap regarding powder segregation in the framework of Northern Indian pharmaceutical production. This study aims to offer significant insights to regulatory agencies and industry stakeholders by investigating the reasons that lead to segregation, evaluating the effects of segregation on product quality, and proposing feasible measures for mitigation. This study is important because it has the potential to improve the consistency and dependability of solid dosage forms, guaranteeing that patients receive medications that adhere to the strictest safety and effectiveness guidelines.

The pharmaceutical sector in Northern India will be briefly reviewed, the significance of solid dosage forms will be discussed, the goals and parameters of the study will be established, and the thesis structure will be presented in this introduction chapter. The approach, data analysis, and conclusions that clarify the intricate problem of powder segregation in the process of producing pharmaceuticals will be covered in detail in the

upcoming chapters. The ultimate goal of this research is to investigate the improvements in pharmaceutical production procedures in Northern India and beyond.

The introduction chapter will outline the following details:

- What is segregation and the effects on solid dosage manufacturing?
- What are the key factors to minimise segregation in the manufacturing of solid dosage forms?
- An overview of the Indian Pharmaceutical Sector in terms with solid dosage manufacturing.

1.1.1. Segregation

In the context of North Indian states' manufacturing of pharmaceuticals, segregation is a vital issue that has to be thoroughly investigated. In the varied and ever-changing terrain of North India, this phenomenon relates to the unwanted separation or non-uniform distribution of components inside medicinal powder mixes. The prevalence and effects of segregation in this area can be attributed to a number of geographical characteristics. First of all, the flow characteristics of powders can be greatly impacted by differences in the temperature and humidity of the various states in North India. The region's varied climate, which may range from arid and hot to cold and humid, can have an impact on how pharmaceutical materials behave when handled and processed.

Moreover, a diverse range of pharmaceutical production facilities, including both smaller as well as more established multinational corporations, may be found in North India. This variation in equipment, infrastructure, and production techniques might affect how segregation is managed and the risk involved. The intricacy of issues linked to segregation is increased by these units' usage of diverse technologies and production techniques. (Deng *et al.*, 2021)

Segregation has serious implications in the pharmaceutical manufacturing industry. It may cause non-uniformity in the content of solid dosage forms, such as tablets and capsules. Patients who obtain such non-uniformity run a significant risk of receiving medications with inconsistent drug content. This may have an effect on how well the treatment works and, in certain situations, raise questions about safety.

Pharmaceutical companies in North Indian states have to deal with these complex issues by applying best practises that are adapted to the unique conditions of the area in addition to following the regulatory requirements established by national organisations like the Drugs Controller General of India (DCGI). Choosing the right blending equipment, maximising mixing durations, managing environmental factors (such as humidity and temperature), and using acceptable excipients to enhance powder flow characteristics are some strategies for reducing segregation. (He *et al.*, 2013)

Adopting strict quality control procedures is also essential. Innovative testing methods, such laser diffraction and near-infrared spectroscopy, can assist in locating and resolving segregation problems at different manufacturing stages, guaranteeing that pharmaceutical goods fulfil the most stringent standards for safety and quality. (He *et al.*, 2013)

A comprehensive strategy that takes into account the region's varied climatic circumstances, manufacturing techniques, and regulatory compliance is needed to address segregation in pharmaceutical production in the North Indian states. To create region-specific policies and support the regular distribution of safe and high-quality pharmaceuticals to the people of North India, cooperation between pharmaceutical companies, regulatory bodies, and research institutes is crucial.

1.1.2. Key factors to minimise segregation in solid dosage form production

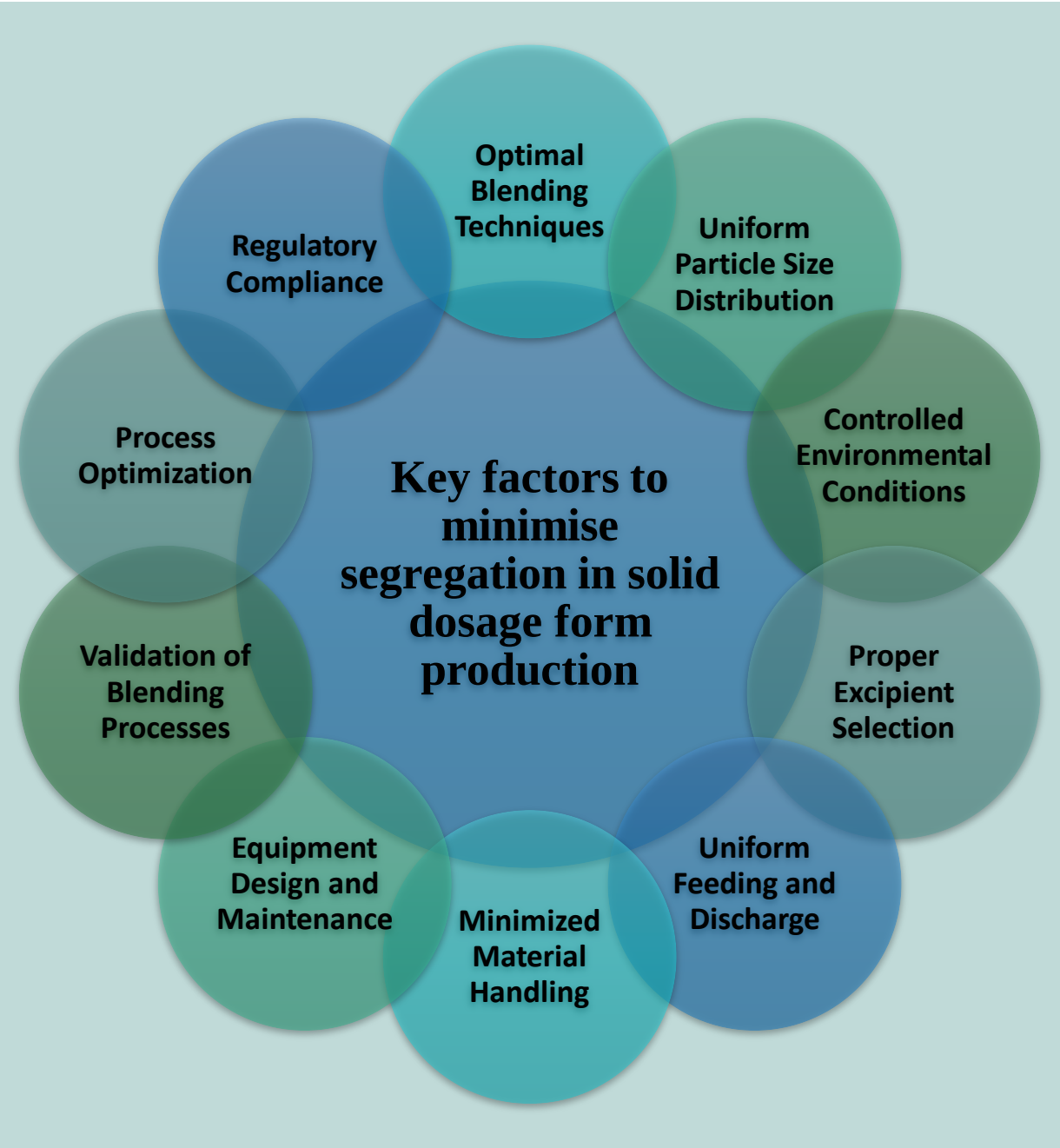

Figure 1: Key factors to minimise segregation in solid dosage form production (Baxter and Prescott, 2009)

To guarantee product quality and consistency, segregation must be minimised during the manufacture of solid dosage forms. The following strategies could help in attaining this goal:

1. **Optimal Blending Techniques:** To accomplish complete and uniform mixing, use the proper blending tools and methods, such as fluid bed mixing or tumble blending. Appropriate mixing durations are vital for achieving an evenly distributed powder mixture.

2. **Uniform Particle Size Distribution:** A comparable particle size distribution should be seen between the excipients and the active pharmaceutical ingredient (API). Ingredients can be properly ground and screened to accomplish this.

3. **Controlled Environmental Conditions:** To avoid moisture absorption and electrostatic charges, which can lead to segregation, maintain consistent temperature and humidity levels in the manufacturing environment.

4. **Proper Excipient Selection:** Select excipients with acceptable flow characteristics and compatibility with the API. Lubricants, glidants, and anti-caking compounds can decrease segregation and enhance powder flow.

5. **Uniform Feeding and Discharge:** Ensure that materials are poured into processing machinery consistently and are released without delays. Blend differences can be introduced via irregular feeding or outflow.

6. **Minimized Material Handling:** Powders should be handled and transported as little as possible since excessive motion and transfer might cause segregation. Install mechanisms for the efficient transport of materials.

7. **Equipment Design and Maintenance:** To avoid errors that might lead to segregation, use equipment that has been well-designed and repair it on a regular basis. Process consistency is ensured by well-maintained equipment.

8. **Validation of Blending Processes:** Perform validation tests on the blending processes to make sure they are reliable and able to provide homogenous powder mixes on a regular basis.

9. **Process Optimization:** To mitigate the possibility of segregation, manufacturing processes should be continuously assessed and optimised. This might entail changing the excipient that is used, the blending apparatus, or the mixing times.

10. **Regulatory Compliance:** Adopt the rules and regulations associated with pharmaceuticals, which mandate content homogeneity and segregation prevention. Compliance guarantees that products fulfil their quality standards.

1.1.3. An overview of the Indian Pharmaceutical Sector in terms of solid dosage manufacturing

The pharmaceutical industry in India, which specialises in solid dosage manufacturing, is a vital component of the country's healthcare system. This industry, which is diverse and large in scope, is essential to the provision of basic healthcare solutions to both the global market and the large population of India. The foundation of India's pharmaceutical sector is the manufacturing of solid dosage forms, such as tablets and capsules, for which the country is internationally recognised for its skill. The nation leads the world in producing high-quality generic medications at competitive prices that cater to a range of medical demands, including sophisticated biologics and pain management. (Shaikh, 2018)

Company Name	Location	Products Manufactured
Sun Pharmaceutical Industries	Vadodara, Gujarat	Pharmaceuticals
Lupin Limited	Mumbai, Maharashtra	Pharmaceuticals
Cipla Limited	Mumbai, Maharashtra	Generic Pharmaceuticals
Torrent Pharmaceuticals	Ahmedabad, Gujarat	Pharmaceuticals
Cadila Healthcare	Ahmedabad, Gujarat	Pharmaceuticals
Alkem Laboratories	Mumbai, Maharashtra	Pharmaceutical Formulations
Glenmark Pharmaceuticals	Mumbai, Maharashtra	Pharmaceuticals

Table 1: Top Pharmaceutical industries in Northern India

The strength of the Indian pharmaceutical industry is derived from its capacity to produce active pharmaceutical ingredients (APIs), hence lowering reliance on imports, in addition to its substantial market share of solid dosage forms. In order to guarantee the safety and effectiveness of solid dosage goods, this industry is subject to strict regulatory control and is

dedicated to quality assurance and compliance with international standards. Additionally, research and development are a major focus for Indian pharmaceutical companies, which promotes innovation in complicated generic formulations and drug delivery systems.

The Indian pharmaceutical industry, which includes manufacturers of solid dosage forms, has proven adaptable and dedicated in the face of international health emergencies like the COVID-19 pandemic by supplying critical drugs and vaccines. In general, the solid dosage manufacturing component of the Indian pharmaceutical industry is a prime example of its contribution to the quality, accessibility, and innovation of healthcare worldwide.

1.2. Research Purpose

The purpose of this study is to investigate at numerous ways that segregation practices affect the pharmaceutical sector in Northern India's production of solid dosage forms. In order to avoid cross-contamination and maintain product quality, segregation—the methodical separation of raw materials and processes—is a crucial component of the pharmaceutical production process. This study's main goal is to examine the segregation techniques currently used by pharmaceutical companies in Northern India and evaluate how well they work to satisfy industry quality standards and regulatory requirements. The purpose of the study is to give insight into how segregation procedures affect the general uniformity, safety, and quality of solid dosage forms. The research also aims to evaluate how well manufacturing processes operate and how well they adhere to Good Manufacturing Practices (GMP) standards. Through addressing the difficulties that manufacturers encounter when putting segregation measures into place, the research aims to provide insights that can guide improvements in manufacturing practices, ultimately improving the quality and compliance with regulations of solid dosage forms in Northern India's pharmaceutical industry.

1.3. Significance of the study

The pharmaceutical sector in Northern India would benefit greatly from this study as it discusses a crucial part of production procedures called material segregation, which has an immediate bearing on the efficacy and security of solid dosage forms. Comprehending the consequences of segregation procedures is essential to guaranteeing pharmaceutical manufacturing that complies with strict industry regulations and industry standards. Through

examining this particular aspect of manufacturing in Northern India, the research hopes to offer insightful information that can result in better product quality, more efficient pharmaceutical production, and greater regulatory compliance. The results of this study might help create best practices for the pharmaceutical business in the area, resulting in a more dependable and safe production environment. In addition, the study's findings could have an impact on industry guidelines, regulatory decisions, and the development of global standards for pharmaceutical production. In the end, this research is important because it can help refine production methods, which will benefit public health by guaranteeing that patients in Northern India and elsewhere receive solid dosage forms that are both safe and effective.

1.4. Research Questions

i. What are the current challenges that pharmaceutical industries face in terms of segregation?
ii. Are there any recent changes which lead to minimising segregation for an effective solid dosage manufacturing process?

1.5. Research Objectives

The overall aim of this thesis is to explore the advancements in solid dosage form manufacturing in terms of minimizing segregation and exploring the Northern-Indian Pharmaceutical Industry.

- To carry out secondary research and review the literature on challenges arising from segregation in the pharmaceutical industries' solid dosage manufacturing operations.
- To assess the techniques that were implemented to limit, reduce, or remove multiple variations of segregation.
- To what extent do issues associated with implementing segregation practices into role affect the productivity and operational procedures of solid dosage form production in Northern India's pharmaceutical industry?

- To utilise the knowledge acquired from secondary research to create a questionnaire, and conduct surveys with subject matter experts in the field, and collect primary research data.
- To assess and summarize the findings from the primary research data and provide a report on comparison to secondary and primary research data.

1.6. Structure of the study

Primary data (an online questionnaire) and secondary data (a literature analysis) are gathered for the current study. The author's understanding of the idea and the advantages that the pharmaceutical industry has gained from implementing techniques to reduce segregation in order to establish sustainable manufacturing operations were enhanced by the published literature. The author received assistance from this critical review in formulating and creating the research questionnaire for the current investigation. Many online searches were used to get the review for the study (Google scholar, Ebsco and PubMed). The data gathered from related journals, papers, and thesis-related publications offers specifics on the concept's current implementation in the industry and emphasises its drivers, challenges, and future possibilities.

The data gathered from the literature on the consequences of segregation in the pharmaceutical industry was used to create the study approach. Using online resources like LinkedIn and different educational organisations, a research questionnaire survey is distributed in order to collect the study's primary data. The specifics taken from the earlier research will inform how the survey questionnaire is structured.

Analysis of the survey responses will yield findings and results that may be used to formulate more insightful conclusions. The discussion focused on the reasons of segregation in the Indian pharmaceutical industry from the viewpoint of the employees.

2. LITERATURE REVIEW

2.1. Overview:

As a dosage form, tablets must have content uniformity (CU) of the active pharmaceutical component to provide consistent medication efficacy. Inadequate mixing and insufficient initial blend homogeneity can lead to a final product that does not satisfy the required uniformity. Alternatively, further particle segregation during storage, transit, or the compression process itself might create this problem. The most associated powder segregation strategies in tablet manufacturing are presented in this review, which also provides an overview of the most recent, readily accessible research on uniformity loss and segregation at the various stages of the production process, including die filling, filling and discharge from the feeding hopper, and blend transfer from the bulk container to the tablet press. (Jakubowska and Ciepluch, 2021)

2.2. Structure of Literature review:

- A detailed description of solid dosage manufacturing.
- A detailed description of segregation mechanisms in the pharmaceutical industry.
- Blend Segregation Phenomena during various phases of the Tableting Procedure
- Modern Perspective: Ensuring Content Uniformity through Continuous Manufacturing

2.2.1. Solid dosage manufacturing

The most common method for drug administration is through oral solid dose forms. The safest and most convenient method of delivery is often provided by oral dose forms. There are several ways to deliver solid dose forms, including tablets, capsules, powders, and cachets.

When it comes to oral dose forms, tablets and capsules are the most frequently prescribed and manufactured. Compared to other dosage forms, tablets provide a number of advantages. Tablets are a type of pharmaceutical dosage form that is solid and can include drug substances with or without appropriate excipients. Depending on the amount of drug components and the intended mode of administration, tablets can have a wide range of shapes, sizes, and weights. Patient compliance may be impacted by the tablets size and shape. (Shaikh, 2018)

i. Active Pharmaceutical Ingredient:

The most typical way that active pharmaceutical ingredients (APIs) are prepared and given to patients is in solid state forms. Tablets are the most often used dose type among the several oral medication items on the market. APIs with appropriate pharmaceutical excipients, such as bulking agents, fillers, binders, and disintegrating agents, make up oral solid dosage forms. It is possible to blend, grind, granulate, dried, tablet, or encapsulate these components. The kind of excipient added to the formulation, the matching product storage stability, and the powder blend qualities all play a role in the successful development of an ideal tablet formulation. For this reason, the preformulation and formulation stages of product development are the focus of this chapter. (Nakamura *et al.*, 2019)

The major points of interest in the preformulation testing discussion are the physicochemical characterisation of the API and excipients, as well as the effects of solubility, stability, and drug-excipient compatibility on the chemical behaviour and therapeutic activity of the finished formulation. Additionally, attention is drawn to how the powder properties of the medication and excipients—such as particle size, shape, flowability, and density—affect the final dosage form's mechanical qualities, disintegration, and dissolution.

ii. Excipients:

1. **Diluents:** They are used to make the dose form larger. Before direct compression, diluents are typically added to tablets with modest doses of the active ingredient to enhance powder flow and compaction characteristics. Typically, diluents are employed in the 5%–80% range. Chemically inert, nonhygroscopic, water soluble, pleasing to the taste, and reasonably priced are all desirable qualities in a filler. Diluents such lactose, starch, calcium phosphate, and microcrystalline cellulose-Avicel (PH 101 and PH 102) are frequently utilised.
2. **Binders:** They are added to tablet formulation to control compressibility and flow properties. Typically, binder is introduced as a dry powder or in solution. The most popular way of adding binders is by adding solution binders, which are pre-made in an appropriate solvent (such as alcohol or water) and added during mixing. The majority of polymeric binders have a hydrophilic character. By making a particle surface more wettable, a hydrophilic binder can help dissolve drugs that are poorly soluble. On the

other hand, an excessive concentration of binders has a detrimental effect on the rate of dissolution and disintegration of tablets. In addition to binder concentration, a number of additional variables, such as binder viscosity, solvent amount, solvent addition technique (open tube or spray), and solvent rate, might have a substantial impact on the range of granule particle sizes and granule hardness. Therefore, it is imperative to optimise these parameters in order to ensure a good wet granulation process. During the direct powder compression or dry granulation process, dry binders are applied to the powder mix. Nevertheless, it has been shown that following the two mechanical treatments (direct compression/roller compaction), binders often lose their tensile strength. Work hardening is the best way to characterise this phenomena. For this reason, choosing the binder for direct compression is crucial in terms of tablet hardness.

3. **Lubricants:** To enhance powder flow characteristics and lower friction during tabletting, pharmaceutical lubricants are utilised. They furthermore assist the tablets in overcoming a number of defects, including as sticking, chipping, and lamination. A range of 0.25%–5.0%, w/w, is added as lubricants to oral solid formulations. Glidants, die-wall lubricant, and antiadherent excipients are the three basic categories into which lubricants are classified. Tablet surfaces and tablet punches do not cling to one another, which is the second type of lubricant action. Tablet ejection and compaction are made easier by die-wall lubricants, which lessen friction between the tablet surface and die wall.
4. **Glidants:** In order to reduce friction between particles and enhance the powder flow characteristics of the materials, glidants are often applied before compression.
5. **Disintegrating agents:** Important excipients known as disintegrating agents help the dosage form disintegrate when it comes into touch with gastrointestinal (GI) fluid. Drug absorption is accelerated as a result of the disintegrating agent's assistance with the start of disintegration. Disintegrants are divided into two categories: super disintegrants (starch glycolate, croscarmellose sodium, microcrystalline cellulose, and colloidal silicon dioxide) and disintegrants (microcrystalline cellulose, alginate, and starch). In an effort to enhance the disintegration processes and produce tablets with better powder compression characteristics and a quicker swelling rate at comparatively low concentrations, super disintegrants were lately produced.
6. **Colouring Agents:** Pharmaceutical excipients, or colouring agents—colorants, pigments, or other terms for inactive substances—are essential to the stability, appearance, and palatability of drugs. These colouring compounds are used to provide

pharmaceutical dosage forms, such liquids, tablets, and capsules unique, identifiable colours. The principal objectives of adding colouring agents to excipients are to enhance patient compliance, simplify product identification, and guard against medication errors. Excipients may contain synthetic or natural colouring agents. Synthetic colourants are made chemically, whereas natural colourants come from plants, minerals, or other naturally occurring materials. Chlorophyll, carotenoids, and beetroot juice are common natural colouring agents. Synthetic colouring agents include a variety of colours that have been authorised by regulatory bodies for use in medicinal applications. The choice of colouring agent is influenced by a number of variables, including the active medicinal component, additional excipients, stability, and solubility. (Nakamura *et al.*, 2019)

7. **Flavouring Agents:** In pharmaceutical excipients, flavouring compounds, often referred to as flavorants, play a crucial role in enhancing the oral dosage forms' overall acceptability and palatability. These forms include suspensions, syrups, orally disintegrating tablets, and chewable tablets. These substances are added to medication products to improve their organoleptic qualities and cover up the taste of some active pharmaceutical ingredients (APIs). The objective is to increase patient compliance, especially for older and paediatric patients who may have trouble swallowing or feel medicine tastes bad. Excipient flavouring agents can be synthetic or natural; their choice depends on a number of parameters, including compatibility, solubility, and stability with other formulation elements.
8. **Coating Materials:** In the production of solid dosage forms, coating agents are essential because they affect the overall stability, look, and functionality of pharmaceutical tablets. Coating agents are applied in thin layers to the tablet's surface during the solid dosage manufacturing process, forming a barrier that is both protective and functional. Coating agents serve the main purpose of masking the taste or odour of the active pharmaceutical ingredient (API) in order to increase tablet palatability. This is especially crucial for drugs that taste bitter or disagreeable.
9. **Adsorbents**: They play a crucial role in the formulation stability and general functionality of pharmaceutical tablets, making them critical excipients in the development of solid dosage products. The purpose of these materials is to improve the therapeutic product's physical properties, including its compression, flowability, and humidity control. Improving powder flow characteristics throughout the production

process is one of adsorbents' main purposes. Variations in tablet weight and content consistency are two problems that might arise from irregularities in powder flow.

10. **Antioxidants**: They are essential excipients used in the production of solid dosage forms because they enhance the stability and durability of pharmaceutical formulations. These additives are used to guard against oxidative deterioration, which can happen when an ingredient is exposed to air, light, or other environmental elements, as well as other formulation components. Drug effectiveness may decline as a result of oxidative deterioration, which can also alter the drug's physical characteristics and produce potentially hazardous by-products.

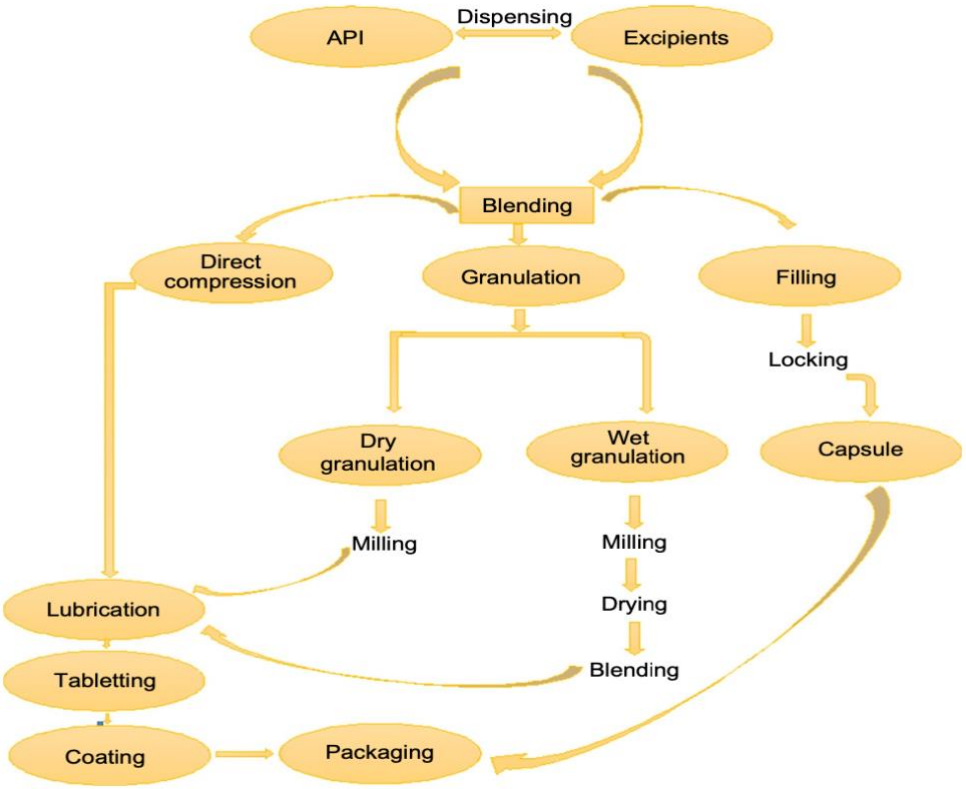

Figure 2: Standard procedure used in the production of solid oral dosage forms (Shaikh, 2018)

Research indicates that tablets larger than about 8 mm in diameter may cause people to have trouble swallowing. Compared to round pills of the same weight, oval tablets may be simpler to swallow and have quicker oesophageal transit times. There are primarily two methods of

manufacturing tablets: moulding or compression. Compressed tablets are typically produced on a large scale, whereas moulded tablets are produced on a smaller scale.

iii. Wet Granulation:

In wet granulation, a granulating liquid—a binder or solvent—is used to create a wet mass based on adhesion processes, which facilitates the agglomeration of powder particles. The quality of the finished product is influenced by a number of factors, including the type of binder, the rate of addition and integration technique, the solubility of the particles in the binder, the speed of the impeller, the kneading components, the duration of the wet massing process, and the temperature of the barrel. Granulation produces free-flowing, dust-free, easily compressible granules, but it is a labour-intensive process that requires several unit operations. To achieve an acceptable quality, several physicochemical properties of the granules, including porosity, moisture, density, size, compressibility, hardness, and content homogeneity, must be within allowable limits. Wet granulation technology has seen several advancements throughout time in terms of tools and procedures. (Nakamura *et al.*, 2019)

Granules have been prepared using twin-screw, fluid bed, and mechanical granulators. Wet granulators with low shear (<150 rpm) and high shear (>200 rpm) are examples of mechanical granulators. For shearing sensitive materials, low shear granulators have been utilised extensively. These granulators also allow granulation and mixing to be done on the same piece of machinery. Commonly used low shear granulators include ribbon and paddle blenders, planetary and rotating-shape mixer/granulators, twin shell or V- blenders, orbiting screw, and sigma-blade granulators. In high shear wet granulation, granulating liquid is sprayed over the powder combination while it is processed in a closed vessel with an impeller spinning rapidly. (Wu *et al.*, 2021)

The fill ratio, impeller characteristics (size, shape, and speed), granulator bowl geometry, and bowl material are among the variables that might alter the mechanical or physical characteristics of the grains produced in a high shear granulator. The shear granulation method has the benefit of using less binding liquid, having quick processing times, and yielding granules with a consistent medication distribution. However, inadequate processing can lead to the production of lumps as a result of over-wetting, as well as the chemical or mechanical deterioration of materials that are delicate or thermolabile. Using atomizers, binder is sprayed as liquid droplets over the powdered materials that have been fluidized.

This causes the ingredients to coat and agglomerate into granules, which are then dried in a drying chamber. This process is known as fluid bed granulation.

Granules are prepared using two designs of fluid bed granulators: top spray and bottom spray/Wurster. Applications using tablet coating have also investigated the Wurster arrangement. Variables in the granule formulation process that affect the quality of granules made using fluid bed granulators include the qualities of the binding liquid, spray rates, and fluidizing air temperatures. In comparison to high shear wet granulators, fluid bed granulators generate granules that are more porous, compressible, and less dense. Nonetheless, the principal constraint of this methodology is attrition-induced size reduction, which can be partially mitigated by employing granulators featuring a tapered design. Furthermore, granules cannot generally be densified by fluid bed granulation, which might be problematic if densification is required to improve flowability. (Shaikh, 2018)

The dual-rotating screws of the twin screw granulator are designed to move the binder and feed material to a designated area, mix them, and then force the resulting mass through revolving dies or a screen to create granules. The introduction of binder, screw design, rotating speed, and the placement of feeders and pumps are some of the variables that affect granule characteristics. The granules made using twin screw granulation have better tensile strength, disintegration, and friability than those made with high shear wet granulation. Wet granulation has advanced through the use of steam, freeze, melt, foam, moist, thermal adhesion, and reverse processes. Very little water (1-4%) is used as a granulating agent in wet or moisture-activated dry granulation.

As a result of the quick processing and drying durations, the procedure is both energy and time efficient. However, this method may not produce a robust granule and is not appropriate for active substances that are hygroscopic or moisture-sensitive. The granulating liquid (water/solvent) used in thermal adhesion granulation is used in small quantities. When using thermal adhesion, the powdered materials are heated to between 30 and 130 degrees Celsius in a closed assembly while being continuously mixed by tumble rotation until granules form. In thermal adhesion granulation, no drying procedure is needed since the powder readily absorbs the granulating liquid during agglomeration because of its tiny quantity. Reduced moisture-associated variabilities as a result of the low binder quantity are a significant benefit of this approach.

However, producing and maintaining heat requires a lot of energy as well as specialised equipment. It is not appropriate for all binders due to its susceptibility to thermolabile chemicals, among other disadvantages. Using water-based steam as a binding medium is known as steam granulation. Steam offers faster and more even diffusion into the powder particles, as well as improved thermal balance throughout the drying process, making this method effective. This approach has limitations, such as the need for large energy inputs to produce steam, which makes it unsuitable for using thermolabile active ingredients.

Agglomerating powder particles using meltable binders is known as melt or thermoplastic granulation. Either a solid that softens and melts during the method (melt-in/in-situ melt granulation) or a molten liquid (spray on approach) can be used to include the melting binder into the powder blend. This technique uses less energy and time since there is no need for the drying and wetting phases when there is no water present. However, using high temperatures might cause formulation components to oxidatively become unstable or undergo thermal deterioration. (Oka, Sahay, *et al.*, 2017)

iv. Dry Granulation:

Pneumatic dry granulation (PDG) is a significant advancement in dry granulation technology. It produces granules with improved flowability and compressibility by utilising a patented pneumatic system in conjunction with the traditional roller compaction approach. In PDG, a roller compactor applies a light compression force to the powder particles to create a compact mass that contains granules and tiny particles. A pneumatic mechanism is used in a fractioning chamber to separate the granules into the proper size range. PDG permits the use of large dosages (70–100%) of drugs. Additional benefits include quick processing times, little to no material waste, compatibility with heat, moisture, and solvent-sensitive medications, and enhanced flow and compressibility. Friability and the effect of recycling on the generated granules' quality are two of the production technique's main limitations. (Römerová *et al.*, 2021)

v. Continuous Manufacturing:

To maintain a consistent hold-up mass during steady-state processing, beginning materials are continually fed into the system and final products are continuously removed from it at the same rate in continuous production. Without any starts or stops in between, every unit activity is integrated into a single manufacturing line. Process analytical technology (PAT) can be used to continuously, regularly, and in real-time monitor the quality attributes of raw materials, intermediates, finished dosage forms, and critical process parameters through measurements made during the process. This will ensure the quality of continuous manufacturing processes. Pharmaceutical companies are currently experiencing a paradigm shift away from batch production and towards continuous manufacturing. This is because continuous manufacturing offers several advantages over batch production, including easier scale-up, robust, and flexible operation, lower risk of variability (which can arise from process discontinuity), smaller footprints, higher-quality products, and safe and dependable manufacturing. However, there are a number of quality and regulatory issues with the continuous manufacturing technique that need to be resolved. These issues include sampling strategy, batch release and recalls, product collection or rejection, raw material traceability, and control strategy. (Shaikh, 2018)

vi. Quality By Design:

The idea of quality by design (QbD) was introduced by the International Conference on Harmonisation (ICH) as a comprehensive method for creating high-quality pharmaceutical goods. The ICH also published a number of regulatory standards. Pharmaceutical QbD is described as a methodical approach to development that is founded on good science and quality risk management, starts with predetermined objectives, and emphasises product and process understanding and control. The QbD method for solid dose projects typically consists of two parts: experiment design, which clarifies the design and control spaces, and Ishikawa analysis, which identifies possible important elements and risks. Many advantages come with QbD, including less generic scepticism from consumers, regulatory flexibility, and quick product launches. Ascertaining medicinal product objectives, identifying important quality, material, and process features, risk assessment, optimisation design selection, design space and optimal formulation identification, and, lastly, developing a control plan for continuous improvement are all included in the QbD framework. (Teżyk *et al.*, 2015)

vii. Process Analytical Technology:

PAT stands for process analytical technology. It is a method for planning, evaluating, and managing production by promptly measuring essential quality and performance characteristics of raw and in-process materials and processes. The ultimate objective is to guarantee superior quality of the finished product. The software system completes the analysis and saves the data, while the hardware takes measurements and makes measurements. PAT can include both basic equipment for inline analysis using Infrared or Raman spectroscopy, as well as more sophisticated devices like an inline pH metre. (Sever *et al.*, 2009)

- Offline: Measurement including the extraction of the sample from the process and its analysis in a laboratory.
- Online: Measurements in which the sample is taken out of the manufacturing process and maybe put back into the production flow.
- Inline: Measurements that can be either invasive or non-invasive and do not involve removing the sample from the process stream.
- At line: Measurement in which the sample is taken out of the process stream, separated from it, and examined within close proximity.

PAT is usually implemented by inserting a probe into the process (such as a reaction vessel) or by allowing process material to flow over a flat probe face (such as granulated product leaving down a product chute). A signal is captured by the probe and sent back to the detector, where it is transformed into a process measurement. Certain PATs allow for fast, consecutive measurements that happen on the order of seconds. These measurements offer process insights and knowledge that standard offline sampling could overlook. Rather than testing quality after the process has been finished, PAT offers the chance to include quality into the process itself. (Sever *et al.*, 2009)

2.2.2. Segregation mechanisms and the causes

Sifting, entrainment of particles in airstream or fluidization (entrainment of air), and rolling segregation are the only significant processes among the thirteen methods of ingredient segregation that have been found in diverse scientific domains for pharmaceutical solids handling. (TANG and PURI, 2004)

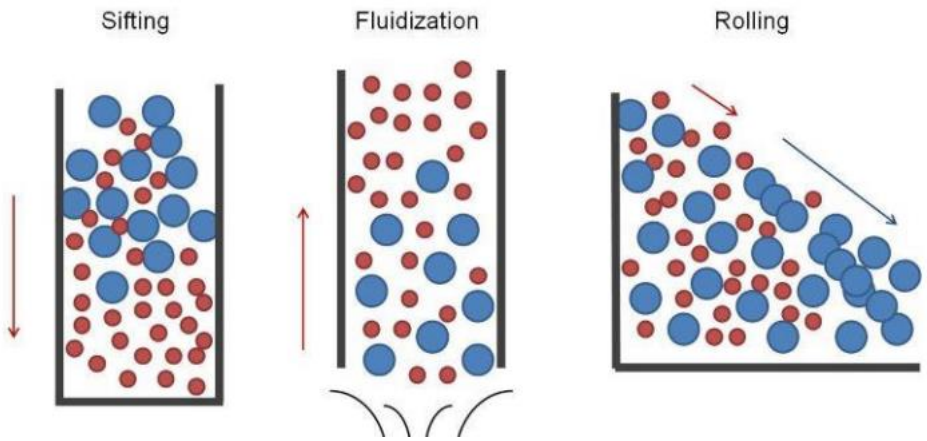

Figure 3:An illustration of the fundamental mechanisms for particle segregation. (Jakubowska and Ciepluch, 2021)

The primary method used for separating components is sifting (also known as sieving or percolation). In this phenomena, smaller particles go through the vacuum spaces in the bed of bigger particles, driven downward by gravity. Larger particles form the upper layer of the powder mass, resulting in an unequal distribution of components throughout. (Oka, Sahay, *et al.*, 2017)

Sifting requires certain requirements to be satisfied.

- In a binary mixture, the separating components' particle size ratio needs to be at least 1.3:1.
- A sufficiently significant mean particle size is present; the precise universal value has not yet been established.
- Freely flowing content
- Differential in velocity between particles in motion

The shape of the apparatus and the kind of flow associated with it determine whether sifting occurs in addition to the characteristics of the material. Funnel flow or mass flow are the two basic ways to describe the flow that occurs during the discharge from a bin or hopper. Funnel flow occurs in hoppers if the walls are too rough or shallow for easy particle sliding, which is an undesired behaviour that leads to particle segregation. There is a "first in, last out" kind of particle movement when the powder along the walls remains stationary while the rest of the

particles flow into a central funnel-shaped channel. In the situation of mass flow (also known as "first in, first out"), where the entire mass is evenly released at the same moment, this issue is not present. Particle segregation caused by funnel flow can be completely avoided by guaranteeing mass flow through appropriate equipment design, for as by using inserts or selecting conical hoppers rather than pyramidal hoppers. (Teżyk *et al.*, 2015)

Another method for segregation in air is fluidization and entrainment, which is dependent on the variation in component particle sizes. Because fine particles have a lower air permeability than coarse particles, air is retained in empty spaces by them for a longer period of time, causing the air to settle on the surface following discharge or during container filling. Similarly, air drag has a greater impact on tiny particles than on bigger particles because they are more susceptible to air counter currents. This leads to their unexpected dispersion, which deviates from estimated trajectories, and their decreased free-fall velocity, which in turn causes the deposition at the top of the falling powder bed. Consequently, the impact of air-induced segregation on mix inhomogeneity differs from sifting in that the powder bed's top layer is composed of finer particles. An alternative demixing mechanism is rolling, which is a more focused form of trajectory segregation in which particles of varying sizes accelerate at different rates because of resistance forces that oppose their momentum at various intensities. Divergent size fractions are therefore dispersed among several areas. For rolling segregation in particular, larger particles deposit along the edges and bottom of the bed because they glide over the powder heap surface more quickly than smaller ones. (Wu *et al.*, 2021)

Regardless of the technique, a critical need for powder segregation is the variation in particle sizes of the mixed elements. It's interesting to note that not much has been written on the importance of polydispersity or size distribution width. On the one hand, it is reasonable to anticipate a greater degree of segregation with larger distributions, as Tang and Puri point out, according to earlier research. However, more recent research on this subject is incongruous, contingent upon the materials under investigation and the process of segregation. For example, mixes with a wider size distribution have been found to be more susceptible to segregation for model non-pharmaceutical blends in vibrating systems or heap formation studies.

Size-induced demixing is thought to be the primary factor, but other blend qualities could also be important. The high flowability of spherical particles may also aid in segregation, as may variations in the particle shapes of the constituents. A density difference may cause trajectory segregation in mixes with comparable particle sizes because heavier particles, for instance,

might sink to the bottom or acquire rolling momentum. The ability of a mixture to aggregate may also represent a component that distorts the interactions; in this case, the size and durability of the aggregate will control the segregation tendency rather than the main particles. (Pernenkil, 2008)

Interestingly, certain mathematical models have been presented that relate the API particle size distribution to the expected content homogeneity of dose forms. For instance, Rohrs suggested a nomograph to find an acceptable mean diameter (d50) value for a given dosage and standard deviation of content. After reviewing the previous models, Hilden developed a more sophisticated model that successfully correlated the impact of individual particle size distribution bins on tablet content uniformity. This model allows RSD to be calculated regardless of the curve shape, based on the dose of the API, true density, and D value that defines the particle size distribution. However, the specifics and the mathematical modelling of the principles of physical segregation, which have been examined, are outside the framework of this study. (TANG and PURI, 2004)

2.2.3. Blend Segregation Phenomena during various phases of the Tableting Procedure

Although process analytical technology (PAT) tools like near-infrared (NIR) spectroscopy have made it possible to monitor changes in API concentration in real-time throughout unit operations, it is still necessary to acknowledge that it is difficult, if not impossible, to conduct in-depth direct investigations into the behaviour of particles in actual industrial equipment and manufacturing processes. This allows for the assessment of blend or final product content uniformity inline or online and the observation of potential issues during the process. Because of this, research on precise demixing behaviour that is important to the pharmaceutical industry typically uses computational techniques like discrete element modelling (DEM) or simulated, reduced experimental settings. (Wu *et al.*, 2021)

It is critical to note that existing capacity constraints require DEM simulations to be simplified. Examples of these simplifications include increasing the size of modelled particles in comparison to actual pharmaceutical blends or encountering difficulties when simulating interactions in multicomponent, polydisperse mixes. Discrete element modelling (DEM) is a useful technique for comprehending the mechanical aspects of particle trajectories, powder flow and segregation in various geometric equipment configurations and under stress conditions during mix handling in tablet production.

When a blend that was initially well-mixed segregates in traditional batch processing, the following sections discuss studies on demixing during three basic operations or handling events: blend discharge from a container or hopper, blend transfer from a container to a tablet press, and blend behaviour during die filling in the tablet compression process. (Shah *et al.*, 2007)

i. Blend Transfer to Tablet Press Feeder from Bulk Container

Evidently, little consideration has been paid to the effects of the blend transfer method on content consistency and segregation in pharmaceutical manufacturing. A powder combination can be carried from an intermediate bulk container (IBC) to a tablet press in three primary approaches during batch processing. A tablet press is positioned above an IBC, and the mix is conveyed to the press's feeding hopper via a chute or a pipe. This is the primary and widely used method of transferring blends. Under such circumstances, the particles may be subjected to air entrainment or fluidization during the free fall in the chute, or sifting or trajectory segregation might occur during the IBC discharge. The second way to deliver a mix is using vacuum suction-powered pneumatic transmission. (TANG and PURI, 2004)

While this approach usually eliminates percolation or flow issues, the fluidization of fines in the pneumatic line may still happen and impact the distribution of API in the press feeding hopper. This effect can be lessened by connecting the conveying line tangentially, as opposed to centrally. In summary, basic manual scooping is a viable technique for blend transfer, wherein a worker fills the hopper with portions extracted from the IBC. The tensions that typically cause sieving or fluidization in conventional transfer methods may be lessened by this labour-intensive strategy, even if it may also have poor reproducibility or considerable dust formation. (Wu *et al.*, 2021)

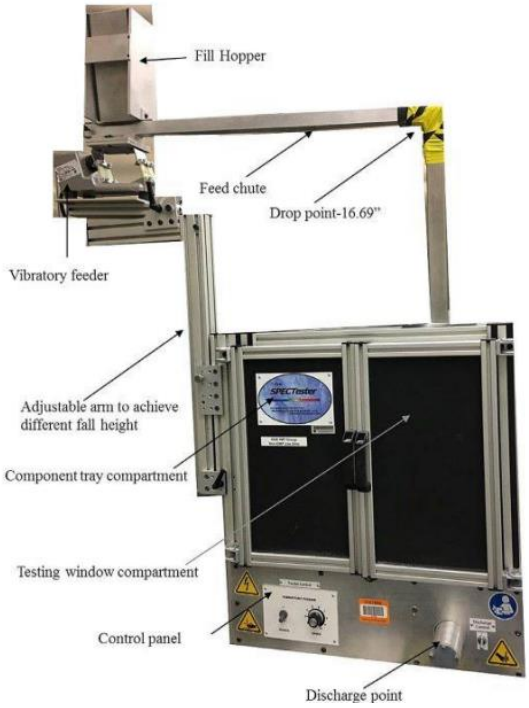

Figure 4: Customised vibratory tester for simulating various segregation methods (Jakubowska and Ciepluch, 2021)

Air-induced gravitational segregation can be minimised by designing equipment optimally, as noted by researchers who have studied powder segregation in vertical chutes. To mitigate the effects of differential drag forces, avoid long drop heights as much as possible. It may also be advantageous to increase pipe diameter. Moreover, the amount or rate of air displacement from the chute can be decreased by reducing the discharge rate by lowering the container outlet diameter or by utilising a rotating valve to drop the powder in smaller increments. The most significant and often used technique, however, is to build an exterior venting system in order to provide an alternate pathway for air to leave beside the powder pile. Increased powder cohesion and decreased flowability might be taken into consideration when feasible, in addition to equipment adjustments. To minimise segregation, however, straightforward fixes like switching to a manual loading mechanism for transfers could be used when more complex steps are not practical. A direct compression blend with two APIs was the subject of an industrial case study that compared two different conveyance methods: directly scooping powder from an IBC with a stainless-steel bowl for manually feeding into a press feeder and discharging from an IBC into a drum with subsequent scooping to replicate the usual gravitational transfer. While the tablets that were compressed from blends that were provided

in both methods met the necessary specifications, one of the APIs showed a notable rise in content at the conclusion of the process, along with higher values of AV and RSD when fed following a gravity transfer replication. However, the problem did not appear when manual loading was used, even if the precise demixing technique was not investigated. The distribution of particles and their mixing index were examined based on their trajectories and velocities in a binary mixture while filling into a conical hopper in DEM simulation research that is generally linked to blend transfer. The three stages of the procedure are as follows: pile-up, steady filling (where segregation occurs), and the first filling of a well-mixed area in the bottom section. In the last stage, it was observed that the larger particles moved farther down the heap towards the hopper sides, while the smaller ones stayed in the middle. In the upper hopper sections and in close proximity to the walls, there was a greater degree of segregation. Generally, the mixing index depended on the estimated sliding and rolling friction coefficients, whereas particle trajectories were determined by rolling for the big portion and bouncing for the smaller one. (Sanjay Kumar Verma *et al.*, 2021)

In relation to the subject of material transfer in the manufacture of solid dosage forms, it should be mentioned that the initial particle size changes brought about by attrition have the potential to cause segregation events. For example, it was discovered that a newly developed API that resists comminution in a tumbling blender and conical mill underwent size reduction and bulk fragmentation when feeding in a horizontal screw feeder. A number of other papers have discussed the attrition of granules in continuous twin screw granulation lines, specifically at the dried granule transfer line and during the wet granule transfer to the fluid bed dryer. The impact of a reduced percentage of "oversized" material and a higher level of fine particles was more noticeable in pneumatic conveyance lines compared to gravitational transfer. Additionally, the final moisture content and formulation composition were linked to the dry material's susceptibility to breaking, so the technique of drying had to be optimised to create strong enough bonds so that the material would not break. Nevertheless, no segregation events related to attrition were evaluated in the publications. (Deng *et al.*, 2010)

ii. <u>Blend Segregation in Hoppers</u>

The phenomenon known as "blend segregation" in hoppers occurs when a combination of particles with varying sizes or shapes tends to separate while being loaded or

unloaded. Hoppers are extensively employed in many different sectors to handle bulk materials, including particles, granules, and powders. When different physical features of the blend's constituent materials cause the components to be separated according to size, density, or other attributes, there is an issue. Particle size distribution, flow characteristics, and hopper design are some of the elements that lead to blend segregation in hoppers. A non-uniform distribution of the mix might result from smaller particles settling into vacuum areas left by bigger particles during the loading and discharge procedures. This may lead to variances in product quality due to irregularities in the composition of the material supplied downstream. By improving hopper design, modifying particle size distributions, and adding flow aids, engineers and researchers aim to minimise blend segregation. Industries may improve the consistency and dependability of their material handling procedures, which will eventually increase the effectiveness and calibre of their production systems, by comprehending the fundamental principles of segregation and using the necessary tactics. (Jivraj *et al.*, 2000)

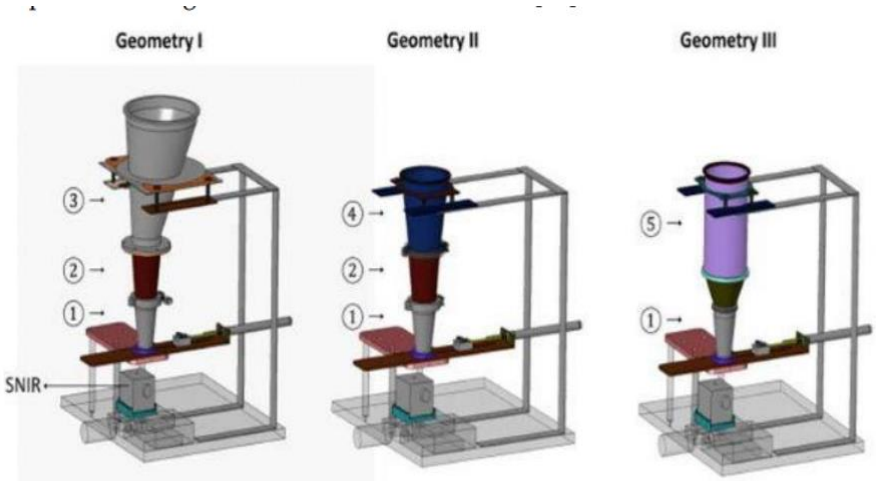

Figure 5:I—asymmetrical conical; II—symmetrical conical; III—cylindro-conical (Jakubowska and Ciepluch, 2021)

When bulk materials leave an eccentric hopper with unequal flow patterns, segregation happens during discharge. An eccentric hopper is named for its off-centre discharge aperture and asymmetrical design. Because of this design, some particles may have

preferred flow routes, resulting in particle segregation according to size, shape, or density. Particle separation may occur during material discharge via the eccentric hopper due to a combination of geometric imperfections and centrifugal forces. Smaller or lighter particles tend to cluster close to the centre of the flow, whereas larger or denser particles may go towards the flow's outer borders. The composition and quality of the material released may be impacted by this segregation's potential to cause an uneven material distribution downstream. In eccentric hoppers, engineers frequently use flow control devices and modifications to the design to overcome segregation during discharge. The negative impacts of eccentricity on particle dispersion can be reduced with modifications to the hopper shape, the addition of devices that promote flow, and careful evaluation of material qualities. Industries may improve the overall efficiency of their material handling processes and encourage more uniform discharge by optimising hopper designs by studying the mechanics of material flow in eccentric hoppers. (Devriendt *et al.*, 2013)

iii. Investigation of Segregation in Rotary Tablet Presses

The investigation of segregation in rotary tablet presses is a critical aspect of pharmaceutical manufacturing to ensure the uniformity and quality of tablet products. Segregation refers to the uneven distribution of components within a tablet formulation, which can lead to variations in drug content and performance. In the context of rotary tablet presses, segregation can occur during the powder blending and compression processes. Factors such as particle size, shape, and density differences among the powder constituents, as well as the mechanical forces exerted during compression, contribute to segregation phenomena. The investigation typically involves a comprehensive analysis of the powder blend and tablet properties, including content uniformity, hardness, and friability. Advanced analytical techniques such as near-infrared spectroscopy and imaging methods may be employed to identify and quantify segregation patterns. Understanding the root causes of segregation allows pharmaceutical manufacturers to implement effective process controls and optimizations, ensuring the consistent production of high-quality tablets with minimal batch-to-batch variability. This investigative approach is integral to meeting regulatory requirements and maintaining pharmaceutical product efficacy and safety. (Jaklič *et al.*, 2015)

2.2.4. Modern Perspective: Ensuring Content Uniformity through Continuous Manufacturing

Lastly, the development of continuous manufacturing needs to be considered in the context of other CQAs and guarantee drug homogeneity. Several studies on continuous direct compression have demonstrated the potential benefits of this approach for improving the CU of solid dosage forms and mitigating blend segregation throughout reduced unit operation steps, among the many other advantages of this approach for current pharmaceutical industry practice. (Hildebrandt *et al.*, 2018)

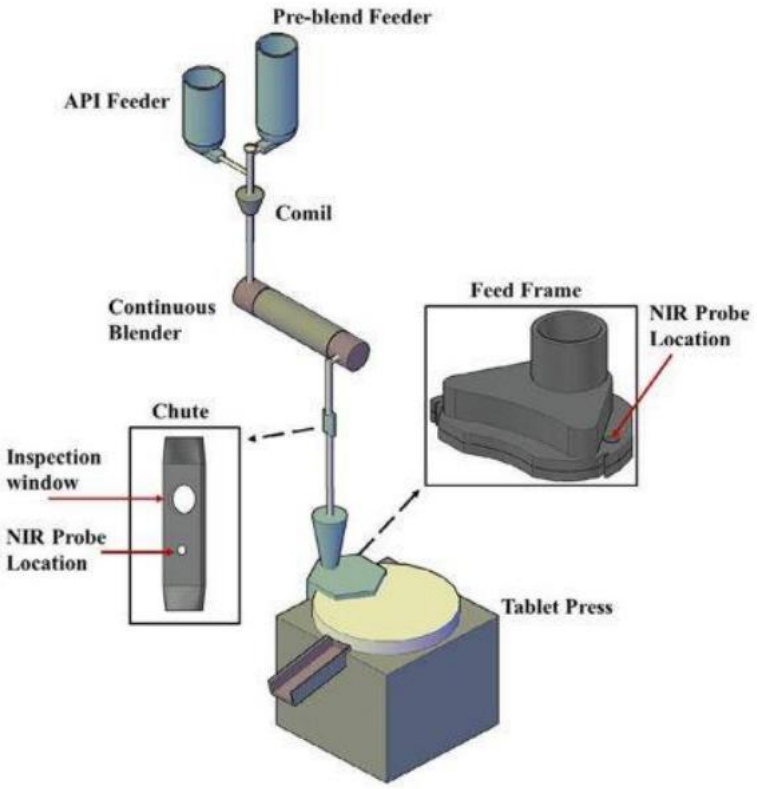

Figure 6:A diagrammatic representation of continuous direct compression (Jakubowska and Ciepluch, 2021)

The pharmaceutical industry uses continuous direct compression, a state-of-the-art production technique, to maximise the Content Uniformity (CU) of solid dosage forms, especially tablets. This method makes it possible for operations to run smoothly and continuously from the mixing of raw materials to the compression of tablets, doing away with the necessity for intermediary procedures like granulation. The careful control over the blending process is the most important component in improving CU. To guarantee homogeneity and a constant amount of the active pharmaceutical ingredient (API) in every tablet during the production process, the powder combination must be continuously mixed. (Jain *et al.*, 2013)

One important component of continuous direct compression is real-time process monitoring. The use of sophisticated monitoring systems allows for quick detection of variations in vital parameters like tablet weight and blend uniformity. This enables quick modifications, guaranteeing that the finished product satisfies exacting quality requirements. Equally important is the accuracy with which raw materials are fed. A major factor in the total CU is the accurate dosing of the excipients and API. With complex feeding systems with accurate controls aid in preserving the consistency of the mixture and, by extension, the content of every tablet. Sophisticated technologies are included in the tablet press control systems to monitor and modify dwell periods, compression pressures, and other critical factors. (Sanjay Kumar Verma *et al.*, 2021)

This degree of control is necessary for maintaining tablet characteristics like weight and hardness constant. Furthermore, uniform blending and effective CU depend on maintaining a stable particle size distribution of raw components, especially the API. A key aspect to keep in mind is to optimise the formulation itself. The resilience of the continuous direct compression process can be increased by using a well-designed formulation and exercising caution when choosing excipients and their ratios. Moreover, a comprehensive Quality by Design (QbD) methodology is often employed, emphasising the comprehension of the influence of many aspects on the quality of the product. This method contributes to the overall performance of continuous direct compression in generating greater Content Uniformity by helping to identify and regulate crucial process factors.

In conclusion, there are a number of benefits to continuous direct compression, such as shorter processing times and cost-effectiveness. However, its ability to improve CU depends on a whole package that includes accurate material feeding, real-time monitoring, exact blending, sophisticated control systems, and a dedication to formulation optimisation via a Quality by Design approach. The manufacturing of pharmaceutical tablets with continuously high Content Uniformity is ensured by this combination of technologies and processes, satisfying the industry's strict quality standards. (Carson, 1988)

2.3. Conceptual Framework

Important factors are covered by the conceptual framework for examining the impact of segregation in the pharmaceutical industry of Northern India while making solid dosage forms. The diverse range of pharmaceutical products, the capabilities of the facility, and the skill of the workers are reflected in the independent variables of personnel training, infrastructure status, and product variety. The dependent variables that measure the efficacy of tactics that are put into practice are the quality of the product and the efficiency of segregation processes. Technology adoption and regulatory compliance are examples of mediating variables that affect the link between independent and dependent variables. The influence of independent factors on segregation practices is moderated by moderating variables, such as supply chain globalisation and firm size. A more comprehensive understanding of the changing environment is offered by contextual factors, which include changes in regulations and industry dynamics. This framework provides a structured strategy for thorough inquiry as it methodically examines the intricate relationships and dynamics influencing the impact of segregation in Northern India's pharmaceutical production.

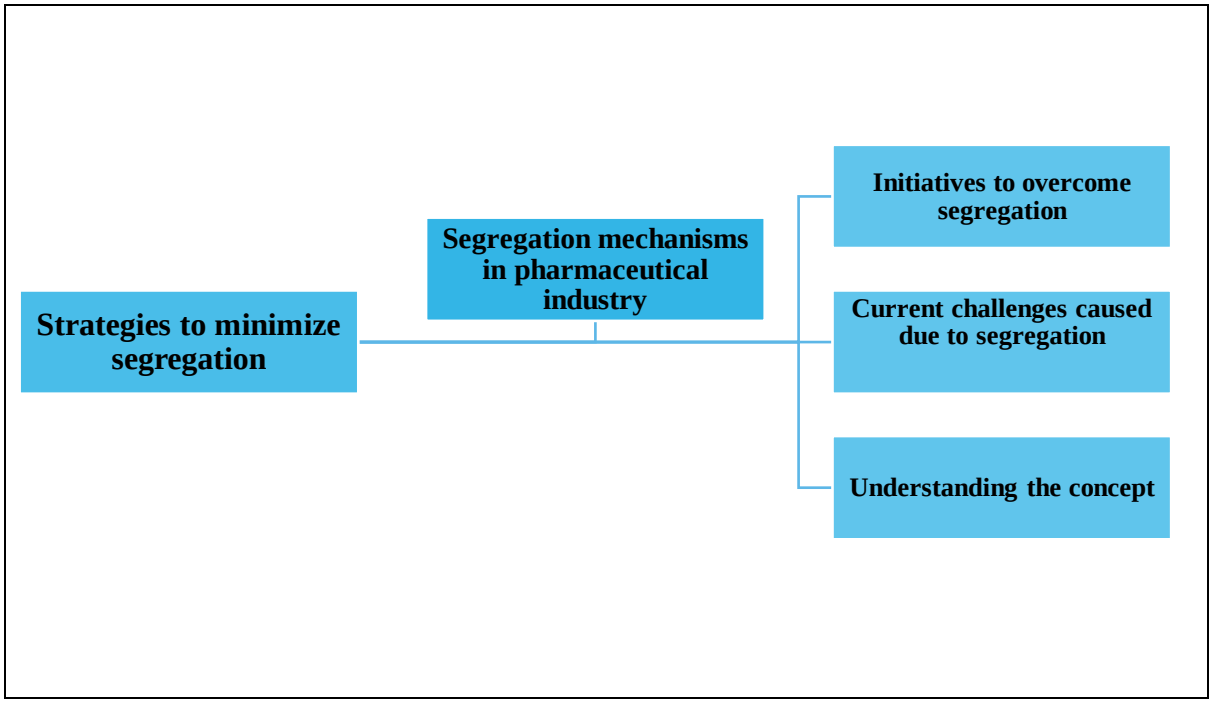

Figure 7: Conceptual framework for the current study

2.4. Summary

The literature study offers comprehensive understanding of the idea of reducing segregation by taking into account the background of motivators, difficulties, and potential future developments. In summary, segregation can significantly affect mediating variables like technological uptake and regulatory compliance. Furthermore, the approach has the potential to improve manufacturing operations' yield and process efficiency. Because of the necessity for sustainable production, the pharmaceutical industry is now encouraging the concept's application.

3. Research Methodology and Design

3.1. Overview

In Chapters 1 & 2 we introduced the basic concept of segregation and its causes in the pharmaceutical industries, specifically concentrating the parts of Northern India. The author concluded that the best approach to use for collecting primary data (quantitative data) for this research topic was a questionnaire survey. This was done in order to gain insights into the critical importance and strategies to minimise segregation in the pharmaceutical sector widely in northern regions of India. Examining the impact of segregation on the Indian pharmaceutical industry is the primary goal of this research project, as the title suggests. Given that the study's focus is on laboratory-level procedures, a variety of perspectives and ideas are sought on this issue from individuals working in manufacturing departments of pharmaceutical companies.

The online survey questionnaire was chosen because it facilitates the evaluation of all of the perspectives held by Indian pharmaceutical workers, allowing for the adoption of measures intended for minimising segregation and providing context for the interpretation of quantitative data. To collect data for the study, an online survey was distributed to one hundred pharmaceutical professionals via LinkedIn and other educational groups. Fourteen open-ended questions covering the effects of segregation and issues encountered by the Indian pharmaceutical company make up the survey questionnaire.

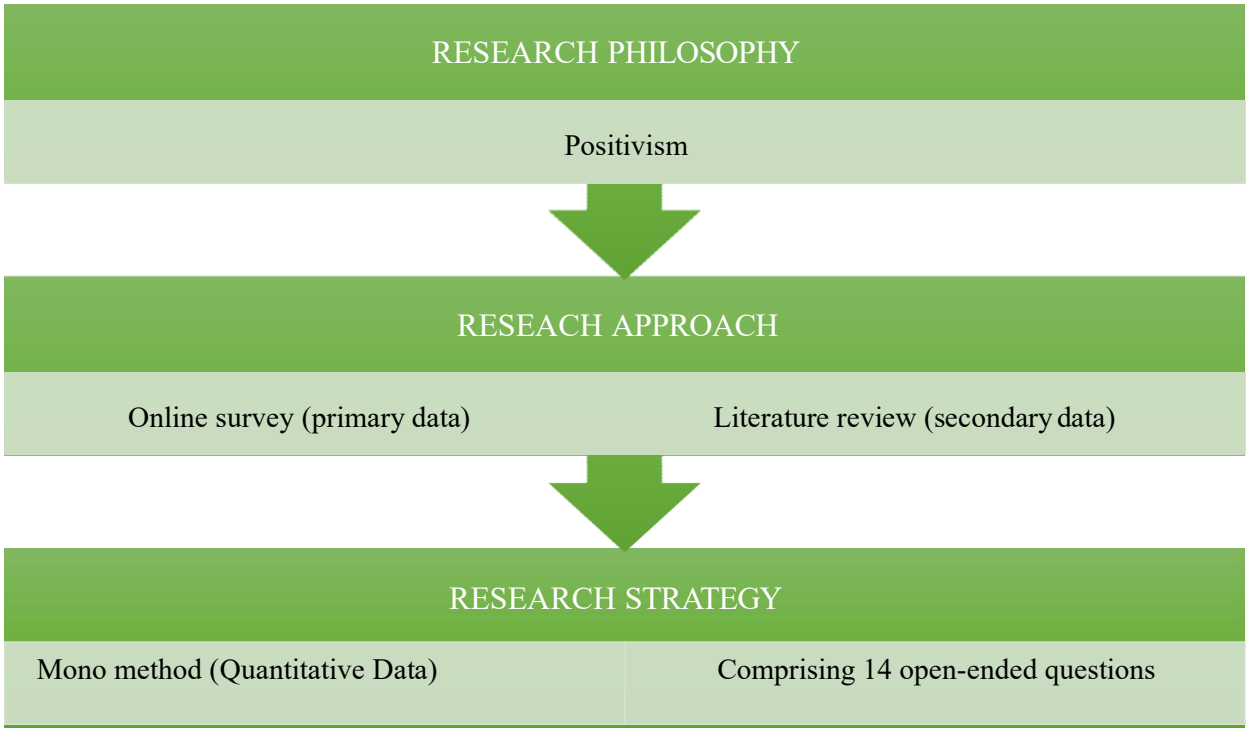

Figure 8:Diagram illustrating the research design

3.2. <u>Research Philosophy and approach</u>

- The research philosophy underlying this research is **Positivism.**

The scientific study of social world is known as positivism. Its objective is to develop general, abstract principles governing the functioning dynamics of the social universe. A law is a statement concerning the interrelationships between the universe's forces. According to positivism, laws must be thoroughly examined against gathered data.

The purpose of this study is to investigate the causes that lead to segregation and control them in order to facilitate reliable manufacturing of dosage forms. From a positivist perspective, objective and empirical research is prioritised. This kind of thinking would look for quantitative correlations between elements, such how segregation affects the pharmaceutical industry. The underlying assumption is that, by means of methodical observation and measurement, discoverable, universal patterns may be found. Large-scale sampling, statistical analysis, and structured surveys with open-ended questions would all be used in the study to determine correlations and

causes. The objective is to produce empirical data that advances knowledge on the impacts of industry segregation in the pharmaceutical sector. The primary hypothesis for the study is planned by taking into account the theories and knowledge derived from actual data; positivism is an appropriate philosophy for this kind of research.

- The most appropriate research strategy for this study is the **Inductive Approach**.

Using an approach known as "inductive research," scientists gather and examine data in order to formulate ideas, conceptions, or hypotheses that are based on trends and observations found in the data. It uses a "bottom-up" methodology, where the researcher begins with specific observations before progressing to broader hypotheses or concepts.

Since the primary research is planned and carried out using the knowledge and theories already in existence on this subject, an inductive technique is appropriate for this study. Examining various literature sources on the subject of segregation's impact on solid dosage manufacture in the pharmaceutical industry helps to define the goals and methods of this investigation. The primary research is initiated by conducting an online survey with open-ended questions that are based entirely on the information gathered from the secondary research.

3.3. Research Strategy

The gathering of secondary data was followed by the collection of primary data, which constituted the study's core.

Collection of Secondary data: Specified search utilising internet databases to find data relevant to the subject.

Several web resources, including Google Scholar, PubMed, EBSCO, and others, were used to collect data for the secondary data used in this study. To complete the secondary research, information about segregation and suitable strategies to reduce it in the pharmaceutical industry was gathered from a number of articles, journals, and relevant thesis studies available on these online platforms. The pieces of literature were published within a decade.

Collection of Primary Data: Through the development and distribution of an online questionnaire.

In order to provide a broad analysis of the impacts of segregation on the manufacture of solid dosage in the pharmaceutical industry situated in India, this study takes into account a number of variables, including understanding of the idea, hurdles, and drivers. In order to gather the data for this study, a questionnaire with open-ended questions on respondents' ideas and opinions on the subject was created. The questionnaire consists of 14 open-ended questions that are intended to analyse specifics about the impacts of segregation, accelerating causes, obstacles, and knowledge of this concept.

The questionnaire is designed and structured with open-ended questions to aid participants in providing justification for their responses that frame the descriptive data and provide a broad understanding of the topic. On particular subjects, participants are free to share their thoughts and opinions. Furthermore, the questionnaire was created in a simple and user-friendly manner, avoiding complexity, so that people could complete it in the estimated 6–10 minutes. To define the closing views of this thesis, the main research data is analysed and findings are evaluated within the context of the available literature.

3.4. Data Collection:

The study's primary data is collected through an **online questionnaire survey.**

The awareness that the studies pertaining to segregation collect quantitative data instead of qualitative data is provided by the literature review's conclusion. In the same manner, quantitative rather than qualitative data are anticipated for this investigation. In order to investigate the use of techniques for preventing segregation in the Indian pharmaceutical industry, data for this study was collected using a questionnaire survey. A survey consisting of 14 questions was developed using Google Forms to conduct the study's survey. The questionnaire was shared online, including through social networking sites like LinkedIn and different English-speaking educational groups, in order to gather the data required for this study.

The questionnaire survey is done with a focus on the cohort working in Indian pharmaceutical industries as the study aims to gather information by analysing the

opinions and views of pharmaceutical experts. The intended respondents for this survey study would be professionals from various departments working in various pharmaceutical businesses in Northern India. These professionals will include those from the quality, regulatory, production and manufacturing, research and development, and so on sectors. The survey form and an official message were sent to each participant, along with a follow-up message to remind them to fill it out. This was the approach used to obtain responses.

To avoid restricting the availability of relevant information on the approaches used to minimise segregation in Indian pharmaceutical industries, the survey was adopted in place of an interview technique in this instance. The secondary research indicates that the interview approach with a limited sample size may restrict the data assessment for this study and will not fully accomplish the objectives needed.

3.5. Access and ethical issues

The survey is going to be conducted in an anonymous, professional manner. All of the questions are generated using particular data about measures to reduce segregation, and aside from a few inquiries about job title and prior experience in the jobs, no additional personal information is requested. The purpose of this is to identify the various departments that answered to the survey.

This information will be useful in screening the data and separate out details to present the study's findings. Participants in the study will be guaranteed anonymity and confidentiality with regard to all information they submit when completing the survey. People are free to participate in or not engage in this survey because it is optional. Additionally, at any point throughout the research, individuals have the option to withdraw from the survey anytime they so want.

3.6. Strategy to Data Analysis

This study's primary data will be subjected to a quantitative analysis. The use of a survey enables respondents to express their opinions openly, without concern, and all at once. It is anticipated that the survey's voluntary responses will provide mono data. To facilitate a

clear and simple analysis of the data, the raw quantitative data from the Google Form is exported straight to Microsoft Excel. Using Google Forms has the benefit of transferring data straight to an Excel sheet, eliminating the need for tedious manual data entry.

3.7. Conclusion:

This chapter's goal is to outline the researcher's fundamental plan and research strategy for carrying out this study. The utilisation of a survey technique for primary data collecting enables the author to acquire quantitative data for the research project. Closed-ended questions provide for greater in-depth insights (less bias) on the research issue, even when the survey is done based only on the researcher's information from earlier publications. The time constraints and the relatively limited sample size of the targeted participants were challenges for the author in finishing the research project.

The results and conclusions from the questionnaire survey are covered in the upcoming chapter. A summary and analysis of the main study findings are provided, using descriptive analysis with percentages and graphical representation. To frame the thesis's concluding views, the primary research data (observations) are analysed within the framework of the published literature.

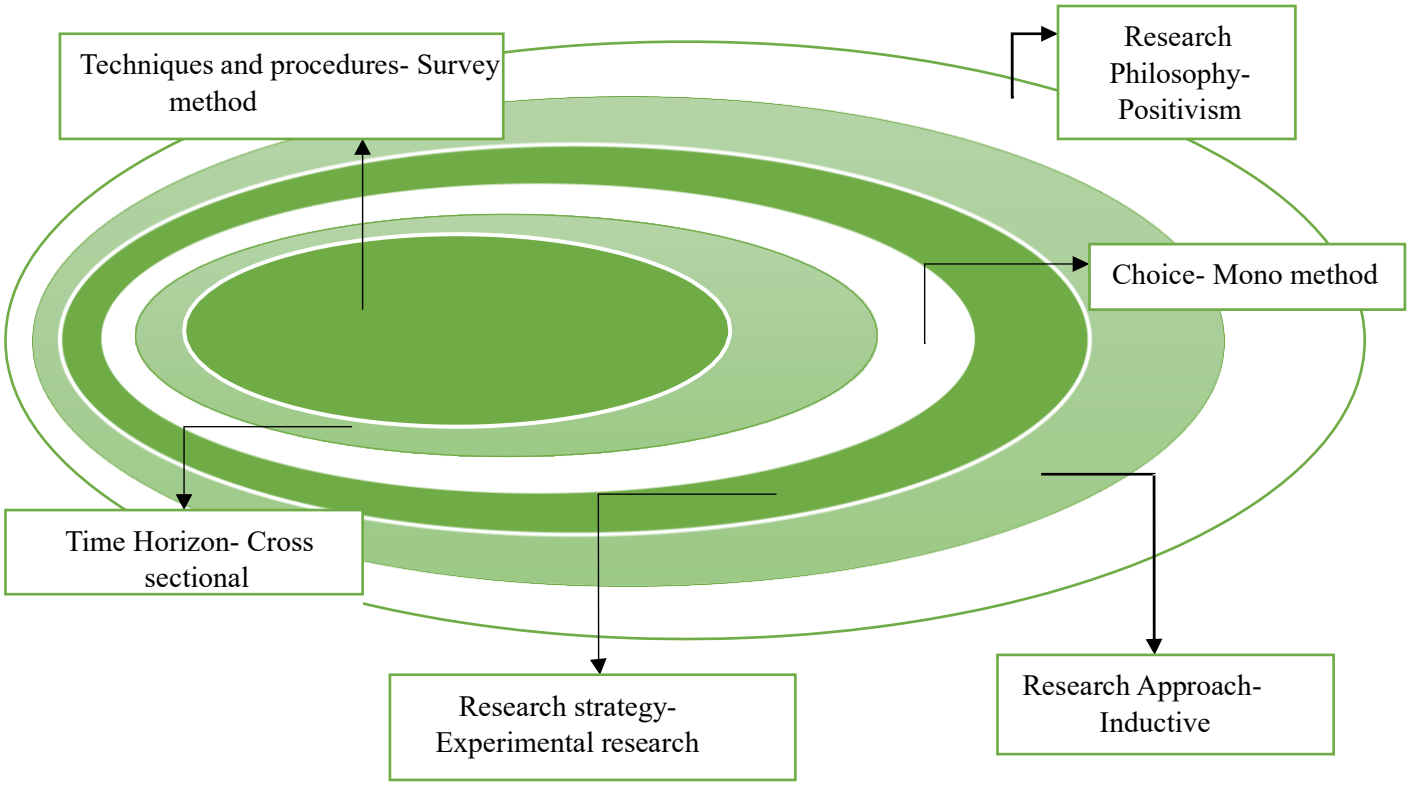

Figure 9:Diagram representing the proposed study using the research onion model (Melnikovas, 2018)

4. Findings and Analysis:

4.1. Overview:

This chapter presents a summary of the study results obtained from an online survey investigating the impact of segregation in the manufacturing of solid dosage forms in the pharmaceutical industries of India, taking into account the driving forces, challenges, and possible future developments. Employee perspectives and opinions about the concept's acknowledgment are also interpreted.

4.2. Findings:

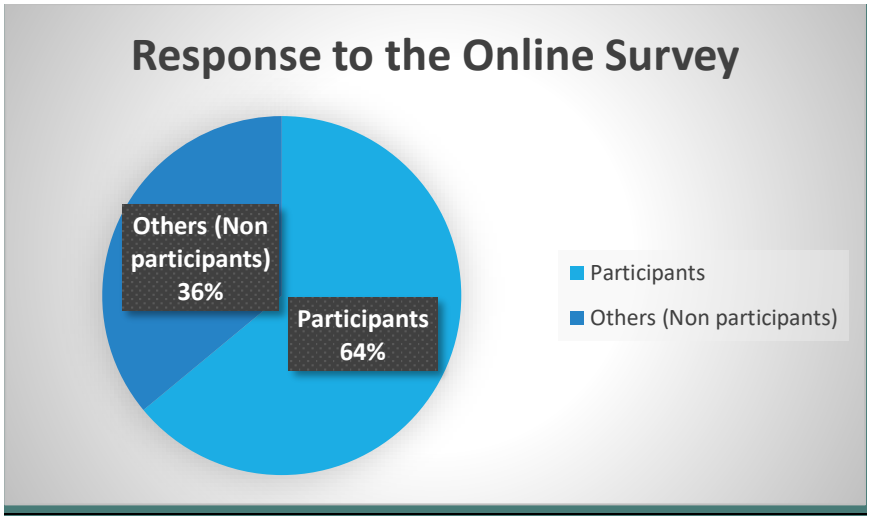

Figure 10: Response of the online survey

In this study, the primary collection of data tool was an online survey using a questionnaire. A total of one hundred (100) pharmaceutical experts working in various divisions of several pharmaceutical organisations throughout Northern India were given the questionnaire via online platforms such as LinkedIn and various educational forums. Remarkably, only sixty-four (64) people responded to the survey study positively.

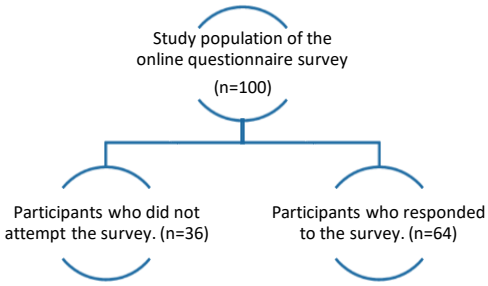

Figure 11:Study demographic

Pharmaceutical industries participated in Online Survey Questionnaire	
Name of Pharmaceutical Industries	**Number of participants**
Alkem Laboratories	**9**
Cadila Healthcare	**8**
Cipla Limited	**12**
Glenmark Pharmaceuticals	**5**
Lupin Limited	**10**
Sun Pharmaceutical Industries	**18**
Torrent Pharmaceuticals	**2**

Table 2: Organisations participated in the survey study

Question 1: Please specify your position or role in the pharmaceutical manufacturing industry?

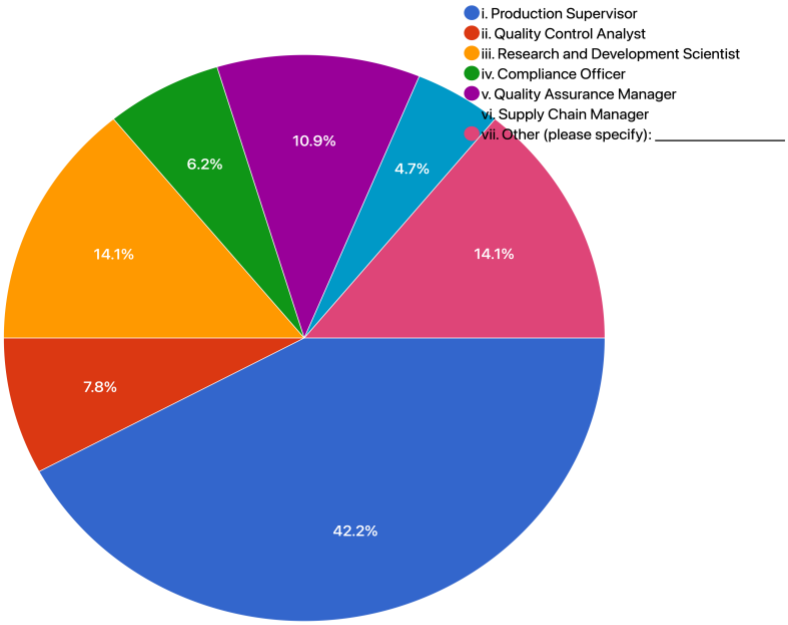

Figure 12: Role/Position in the Pharmaceutical Sector

Roles/Position in the Pharmaceutical Industry	Number of participants	Response Rate (%)
Production Supervisor	27	42.2%
Quality Control Analyst	5	7.8%
Research and Development Scientist	9	14.1%
Compliance Officer	4	6.2%
Quality Assurance Manager	7	10.9%
Supply Chain Manager	3	4.7%
Other	9	14.1%

Table 3: Role/Position in the Pharmaceutical Sector

This question mainly targeted to the employees working in the pharmaceutical manufacturing unit as they would have much more emphasis on the concept of segregation. It is observed that the highest percentage of the responses received was from respondents working as "Production Supervisor" which is at 42.2%. Surprisingly, the same percentile of responses received from respondents working in different roles at about 14.1% which come under the role as "Research and Development Scientist" and in "Other" respectively. The third highest percentile of respondents belonged to the role of "Quality Assurance Manager" at 10.9%. The least responses received was from the respondents working as "Supply Chain Manager" at 4.7%. Moreover, two more set of responses which were found to be 7.8% and 6.2%

were received from respondents who work under the respective roles "Quality Control Analyst" and "Compliance Officer".

Question 2: How many years of experience do you have in solid dosage manufacturing within the pharmaceutical industry?

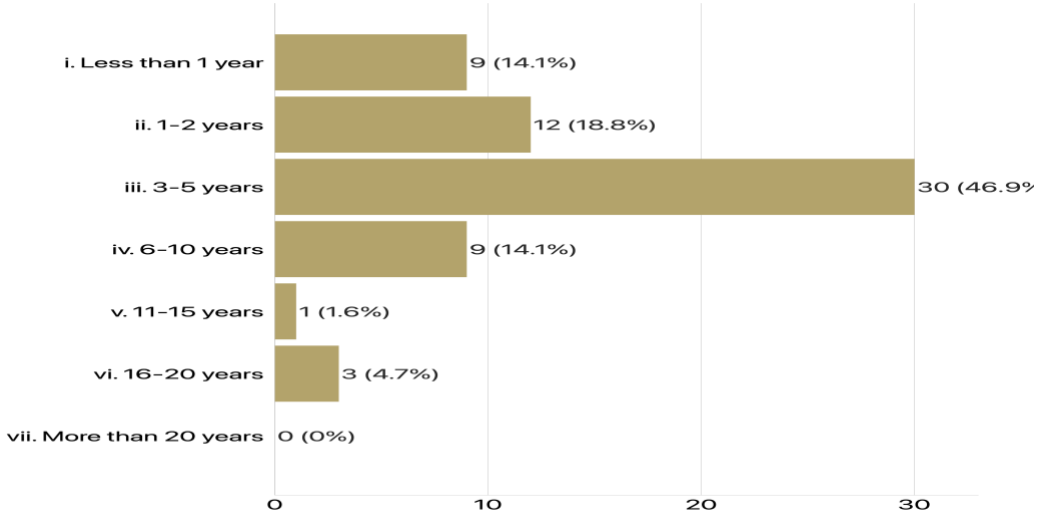

Figure 13:Years of experience in the job role

Work Experience	Number of respondents	Response rate (%)
Less than 1 year	9	14.1%
1-2 years	12	18.8%
3-5 years	30	46.9%
6-10 years	9	14.1%
11-15 years	1	1.6%
16-20 years	3	4.7%
More than 20 years	0	0%

Table 4: Years of experience in the job role

The purpose of this study aims to investigate Indian pharmaceutical industries' interest in implementing strategies to reduce segregation. To elicit precise and lucid responses, the question was phrased in an open-ended approach. The findings showed that most industries do, in one way or another, support measures to reduce segregation in order to encourage environmentally friendly and sustainable manufacturing practices.

The purpose of this question was to know how much experience the respondent has secured in the manufacturing field in order to have a better understanding on the topic. Surprisingly, majority of the respondents have an experience in the time limit (3-5 years) which is around 46.9% of the total response rate. There were no respondents who have had an experience in the time limit (More than 20 years). The second highest response received was from respondents who work under the time limit (1-2 years) which is at 18.8%. About 9 respondents who have less than a year experience has participated in the survey and the response rate is found to be similar to that of respondents who have work experience (6-10 years). The most qualified 3 respondents were found to have a work experience (16-20 years) and the response rate was found to be around 4.7%. There was only 1 respondent from the work experience criteria (11-15 years) and the response rate was found to be around 1.6%.

Question 3: Please rate the overall impact of segregation on solid dosage manufacturing in your opinion?

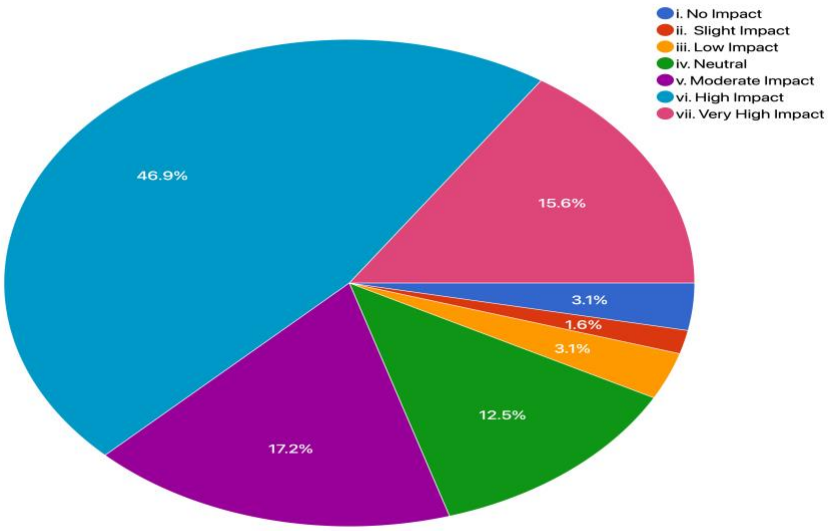

Figure 14: Overall impact of segregation in solid dose manufacturing

Impact of segregation on solid dosage manufacturing	Number of Participants	Response Rate (%)
No Impact	2	3.1%
Slight Impact	1	1.6%
Low Impact	2	3.1%
Neutral	8	12.5%
Moderate Impact	11	17.2%
High Impact	30	46.9%
Very High Impact	10	15.6%

Table 5: Overall impact of segregation in solid dose manufacturing

Surprisingly, about 2 participants responded that there is no impact of segregation on solid dosage manufacturing and the response rate was found to be about 3.1%. All the other

participants admitted that there was even a slight impact caused due to segregation. Starting with 1 participant believed that there was a slight impact, and the response rate was found to be 1.6%. However, 2 participants also believed that there was a low impact of segregation on pharmaceutical manufacturing process, which also had a response rate of 3.1%. Furthermore, there were about 8 participants who neither agree nor disagree to the impact of segregation on manufacturing procedures. The majority of the participants believed that there was a high impact of segregation in solid dosage manufacturing. The response rate for these 30 participants was found to be 46.9%. There were 2 other group of participants one who supported for moderate impact caused by segregation. They were found to be 11 in number and the response rate was found to be 17.2%. There were a last group of participants around 10 in number who were also to be supporting the impact of segregation on solid dosage manufacturing on a much higher level. Thereby, it is clear that from the responses obtained from the study that there is a high impact of segregation on solid dosage manufacturing.

Question 4: To what extent do you believe that employees are adequately trained and aware of segregation issues in the manufacturing process?

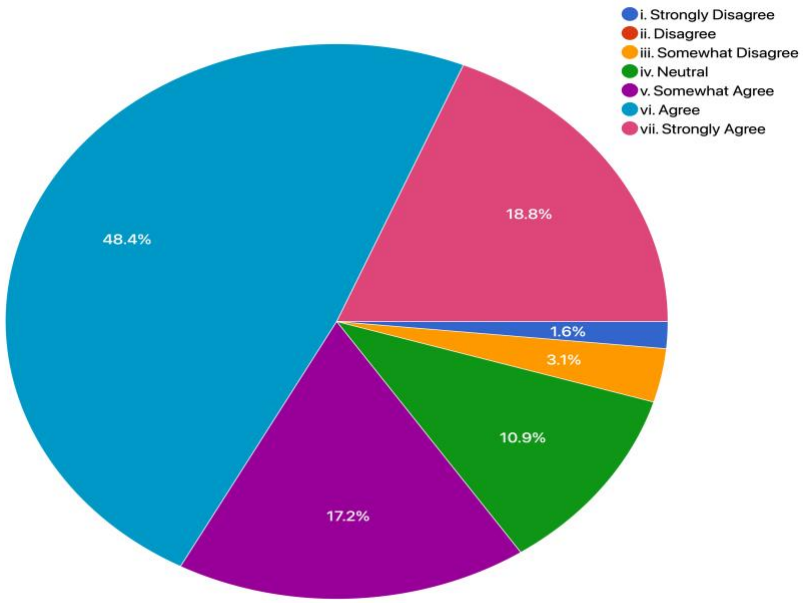

Figure 15: Adequate training and awareness of segregation in manufacturing process

Employee awareness of segregation concerns/ training provided	Number of participants	Response Rate (%)
Strongly Disagree	**1**	**1.6%**
Disagree	**0**	**0%**
Somewhat Disagree	**2**	**3.1%**
Neutral	**7**	**10.9%**
Somewhat Agree	**11**	**17.2%**
Agree	**31**	**48.4%**
Strongly Agree	**12**	**18.8%**

Table 6: Adequate training and awareness of segregation in manufacturing process

The findings show that about 31/64 participants who responded agree to the fact that they are aware of the concerns caused by segregation in the pharmaceutical industry and adequate training has been provided by the pharma industries they have been employed. The response rate was found to be the highest for the above-mentioned participant category which is 48.4%. One of the participants strongly disagree which helps us to understand the lack of knowledge on the subject. There are about 2 participants who somewhat disagree, and the response rate was found to be only about 3.1%. There were about 7 participants who neither agree nor disagree to the employee awareness of segregation concerns in the production process. 11 participants somewhat agree to the above mentioned and the response rate was found to be 17.2%. Lastly, about 12 participants also strongly agree to the concerns caused by segregation and the adequate training has to be provided for the same in order to have a better understanding of the production process. It is evident from the table that the majority of the participants agree they have better understanding and awareness of the concerns of segregation.

Question 5: How do you perceive the impact of segregation on the overall efficiency of solid dosage manufacturing?

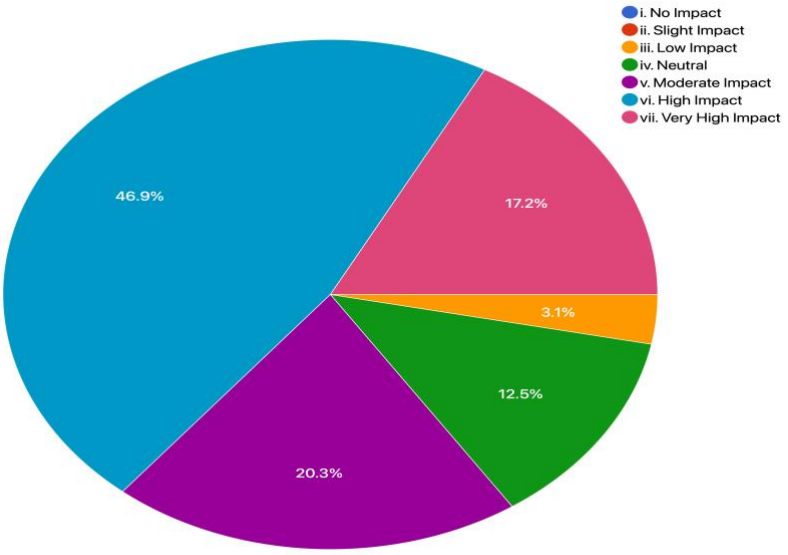

Figure 16: Impact of segregation on the overall efficiency of solid dosage manufacturing

Impact of segregation on overall efficiency of solid dose manufacturing	Number of Participants	Response Rate (%)
No Impact	**0**	**0%**
Slight Impact	**0**	**0%**
Low Impact	**2**	**3.1%**
Neutral	**8**	**12.5%**
Moderate Impact	**13**	**20.3%**
High Impact	**30**	**46.9%**
Very High Impact	**11**	**17.2%**

Table 7: Impact of segregation on the overall efficiency of solid dosage manufacturing

It is evident that the majority believe that there is an impact of segregation on overall efficiency of solid dose manufacturing. About 30/64 participants who responded support that there is a high impact on the above mentioned. As we know that even a slight variation in the manufacturing process can have serious issues with the efficacy of the final product. Surprisingly, no participant responded to no impact or slight impact for the survey study. The least number of participants support that there is a low impact, and the response rate was found to be 3.1%. In this study around 8 participants neither agree nor disagree to the impact of segregation on overall efficiency. The response rate for those 8 participants was found to be 12.5%. 13 participants believed that there was a moderate impact of segregation on the overall production process and the response rate was found to be 20.3%. Lastly, about 11 participants only responded for very high impact and the response rate was found to be 17.2%.

Question 6: To what extent does segregation influence production timelines and delivery schedules?

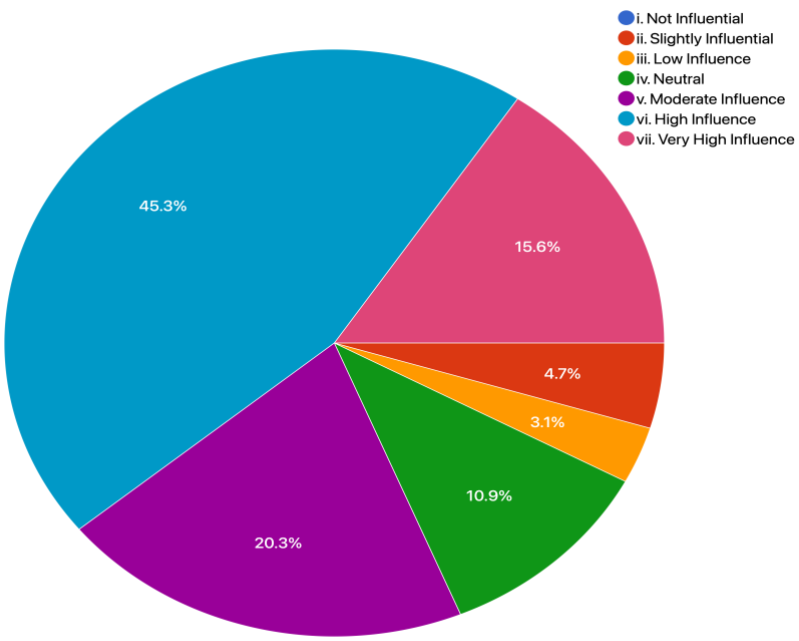

Figure 17: Extent of influence on production timelines and delivery schedules due to segregation

Influence of segregation on production timelines & delivery schedules	Number of Participants	Response Rate (%)
Not Influential	**0**	**0%**
Slightly Influential	**3**	**4.7%**
Low Influence	**2**	**3.1%**
Neutral	**7**	**10.9%**
Moderate Influence	**13**	**20.3%**
High Influence	**29**	**45.3%.**
Very High Influence	**10**	**15.6%**

Table 8: Extent of influence on production timelines and delivery schedules due to segregation

As we discussed how segregation has an impact on overall efficiency in Question 5, similarly here in the question it helps us to understand the extent segregation has an impact on delivery schedules and production timelines. About 29/64 participants responded that there is a high influence of the above mentioned on the production protocols. The response rate for those 29 participants was found to be 45.3%. There is no participant who believes that segregation is not influential on the manufacturing process in pharmaceutical industries. About 3 participants believe that the impact of segregation on production timelines is slightly influential and the response rate was found to be 4.7%. Participants who responded to low influence in relation to the extent of segregation on the pharmaceutical manufacturing procedures, the response rate for the same was found to be 3.1%. Participants who neither agree nor disagree to the fact that segregation does have an impact on solid dose manufacturing were found to be 7 with the response rate of 10.9%. 20.3% was the response rate for the participants who believed that there was a moderate influence in terms of segregation with relation to production timelines and delivery schedules. Only 10 participants supported with very high influence of segregation in pharmaceutical manufacturing industry.

Question 7: How effective are the existing quality control measures in detecting and addressing segregation issues?

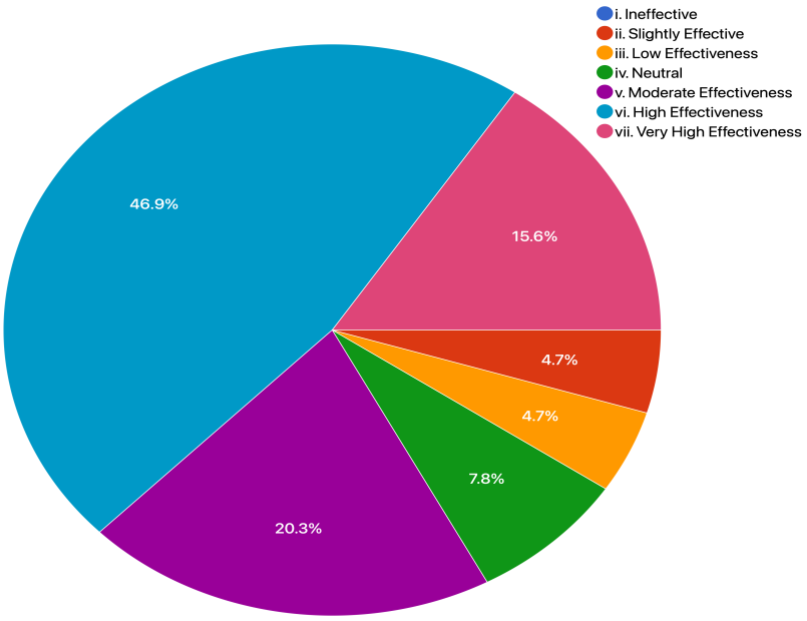

Figure 18: Existing quality control measures in detecting and addressing segregation issues

Effectiveness of existing quality control measures in addressing segregation issues	Number of Participants	Response Rate (%)
Ineffective	0	0%
Slightly Effective	3	4.7%
Low Effectiveness	3	4.7%
Neutral	5	7.8%
Moderate Effectiveness	13	20.3%
High Effectiveness	30	46.9%
Very High Effectiveness	10	15.6%

Table 9: Existing quality control measures in detecting and addressing segregation issues

The existing quality control measures in detecting and addressing segregation issues was found to have high effectiveness for about 30 participants and the response rate was highest for this set of participants which was found to be 46.9%. Surprisingly, no participants found it ineffective in terms of existing quality control measures in addressing segregation issues in the pharmaceutical industries. However, the same number of participants found the response as both slightly effective and low effective, and their response rate was found to be 4.7%. About 5 participants neither agree nor disagree to the effectiveness of existing quality control measures and the response rate was found to be 7.8%. Nearly, the response rate was 20.3% for 13 participants, find it moderately effective regarding segregation issues in the pharmaceutical manufacturing industry. Surprisingly, only 10 participants responded to very high effectiveness of the existing quality control measures for addressing segregation issues in the pharma industries. Thereby, it is evident that the existing quality control measures in detecting and addressing segregation issues are highly effective.

Question 8: To what extent does segregation affect the overall cost of manufacturing solid dosage forms?

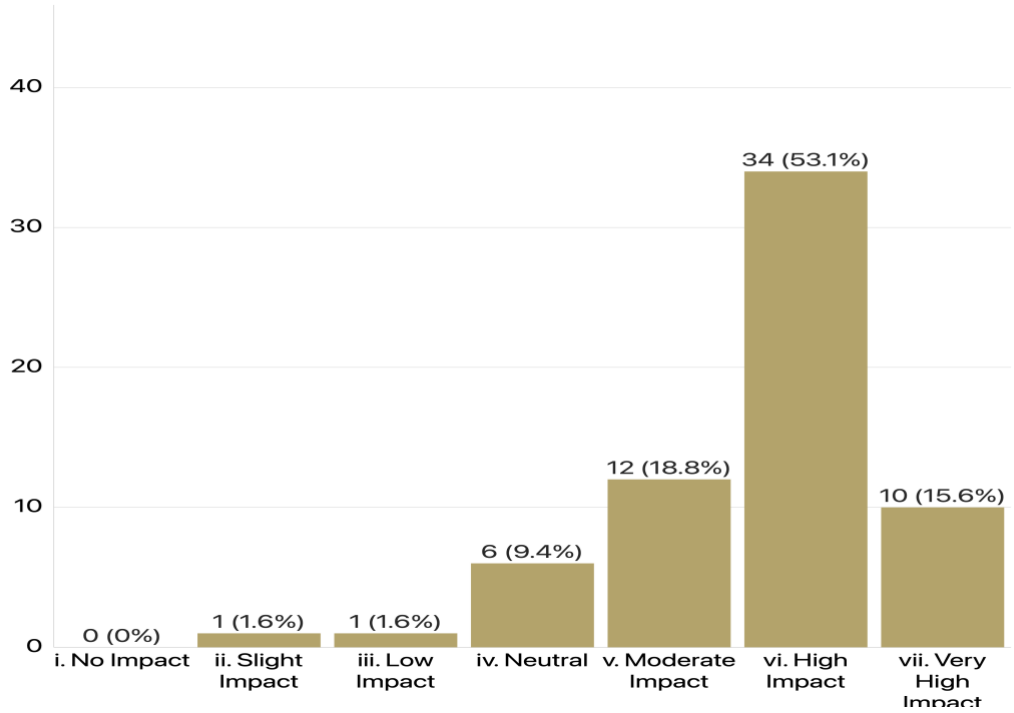

Figure 19: Segregation affect the overall cost of manufacturing solid dosage forms

Overall effect of segregation on cost of manufacturing	Number of Participants	Response Rate (%)
No Impact	0	0%
Slight Impact	1	1.6%
Low Impact	1	1.6%
Neutral	6	9.4%
Moderate Impact	12	18.8%
High Impact	34	53.1%
Very High Impact	10	15.6%

Table 10: : Segregation affect the overall cost of manufacturing solid dosage forms

In this question there were no responses received for no impact for the overall effect of segregation on the cost of manufacturing. One participant each believed that there was a slight impact or low impact of segregation on the cost of manufacturing for which the response rate was found to be 1.6%. Six of the participants who neither agree nor disagree to the overall effect of segregation on cost management with a response rate of 9.4%. Moderate impact was the response from about 12 participants for the impact on pharmaceutical cost over the production procedures. Surprisingly, only 10 participants believed that there was a very high impact for the same as mentioned from the table provided and the response rate was found to be 15.6%.

One important factor to take into account in the production of pharmaceuticals is the degree to which segregation influences the total cost of producing solid dosage forms. The efficiency and quality of the manufacturing process may be significantly impacted by segregation, which is the separation of powders or granules depending on particle size, density, or other properties. There is a wide range of effects on costs. To begin with, segregation may result in inconsistent drug content in the finished product, requiring more testing and quality control procedures, which raises the manufacturing cost overall. Strict segregation regulations further complicate the manufacturing setup by calling for specialised tools and closer supervision,

which raises the cost of capital and operating costs. Thereby, there is a high impact by the effect of segregation on the cost of manufacturing.

Question 9: How does segregation influence the overall product yield in solid dosage manufacturing?

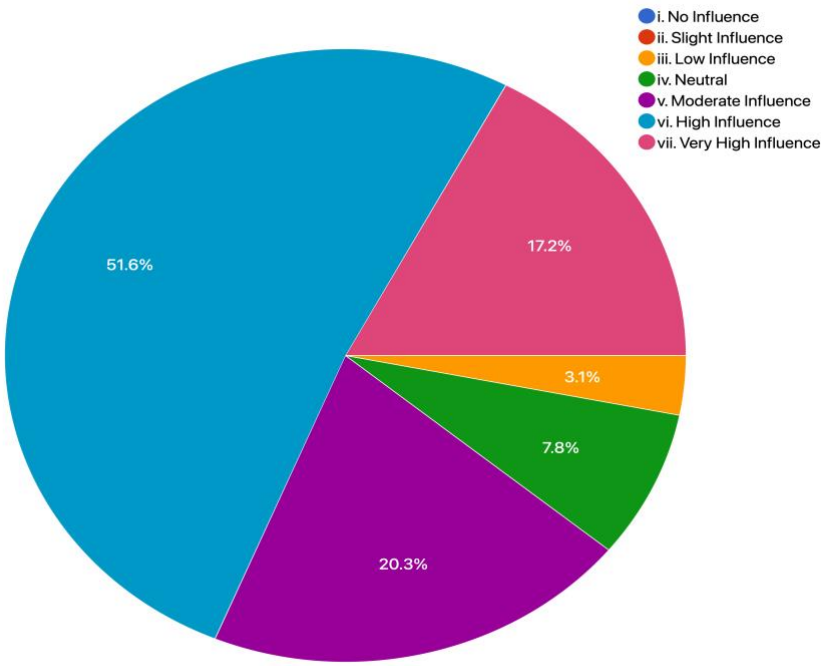

Figure 20: Segregation influence the overall product yield in solid dosage manufacturing

Influence on product yield due to segregation	Number of Participants	Response Rate (%)
No Influence	0	0%
Slight Influence	0	0%
Low Influence	2	3.1%
Neutral	5	7.8%
Moderate Influence	13	20.3%
High Influence	33	51.6%
Very High Influence	11	17.2%

Table 11: Segregation influence the overall product yield in solid dosage manufacturing

From the responses received for this question it is found that there were no participants who responded “no influence” or “slight influence” for the influence on product yield caused due to segregation. About 2 participants also responded to low influence and the response rate was 3.1%. However, the highest response rate (51.6%) was received for high influence from about 33 participants in the survey study. About 5 participants who neither agree nor disagree to the influence on product yield due to segregation which brings the response rate to 7.8%. Participants (13/20.3%) who believed that there was only moderate influence due to segregation on product yield. Very high influence due to segregation on product yield was the response of participants who responded positive to this response (11/17.2%). From the 64 responses about 33 responded to high influence on product yield due to segregation.

In solid dosage production, segregation is crucial in determining total product yield and has a significant impact on the final pharmaceutical product's uniformity and quality. Dosage uniformity can be severely compromised by segregation, which occurs when particles with different properties, including size or density, separate during the production process. The formulation's uneven dispersion of excipients and active pharmaceutical ingredients (APIs) may result in variations in the amount of medication in each dose, jeopardising the product's overall quality. The effects also extend to the effectiveness of blending procedures, affecting the mixture's homogeneity. As a result of segregation, incomplete blending can lead to localised concentrations of components, which can impact compressibility and particle size distribution during tablet manufacturing.

Question 10: How often does segregation lead to deviations or non-compliance with regulatory requirements?

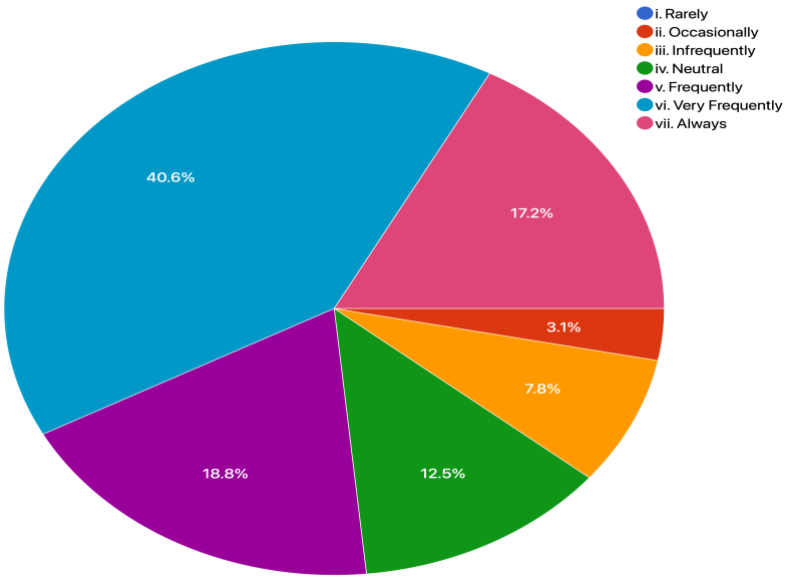

Figure 21: Segregation lead to deviations or non-compliance with regulatory requirements

Non-compliance with regulatory requirements due to segregation	**Number of Participants**	**Response Rate (%)**
Rarely	**0**	**0%**
Occasionally	**2**	**3.1%**
Infrequently	**5**	**7.8%**
Neutral	**8**	**12.5%**
Frequently	**12**	**18.8%**
Very Frequently	**26**	**40.6%**
Always	**11**	**17.2%**

Table 12: Segregation lead to deviations or non-compliance with regulatory requirements

From 64 responses about 26 of the participants supported that there was a possibility of deviation or non-compliance with regulatory requirements due to segregation. The response rate was the highest and it was found to be 40.6%. No participants responded positive to the

response “Rarely”. Moreover, only 2 participants (3.1%) believed that this was occasionally only applicable for deviations caused by segregation. About 5 participants responded openly that the deviations caused due to segregation was infrequent and the response rate was found to be 7.8%. 8 participants neither agreed nor disagreed and the response rate was found to be 12.5%. Simultaneously, nearly the same number of participants also responded to two different responses, 12 of 64 (18.8%) responded that segregation frequently led to deviations with regulatory requirements. 11 of 64 (17.2%) were the only ones that responded segregation always led to deviations with regards to regulatory requirements in the pharmaceutical environment.

In pharmaceutical production, the likelihood that segregation would result in deviations from or non-compliance with regulatory standards varies depending on a number of factors, such as the kind of manufacturing process, the efficacy of quality control systems, and the use of best practices. The homogeneity of drugs composition in solid dosage forms—a crucial factor that health authorities regulate—may be jeopardised by segregation. Segregation may cause deviations from the required content uniformity standards if it is not sufficiently handled, which might result in a non-compliance with regulatory requirements.

Question 11: To what extent are segregation-related challenges promptly addressed, preventing long-term consequences on product quality and regulatory compliance?

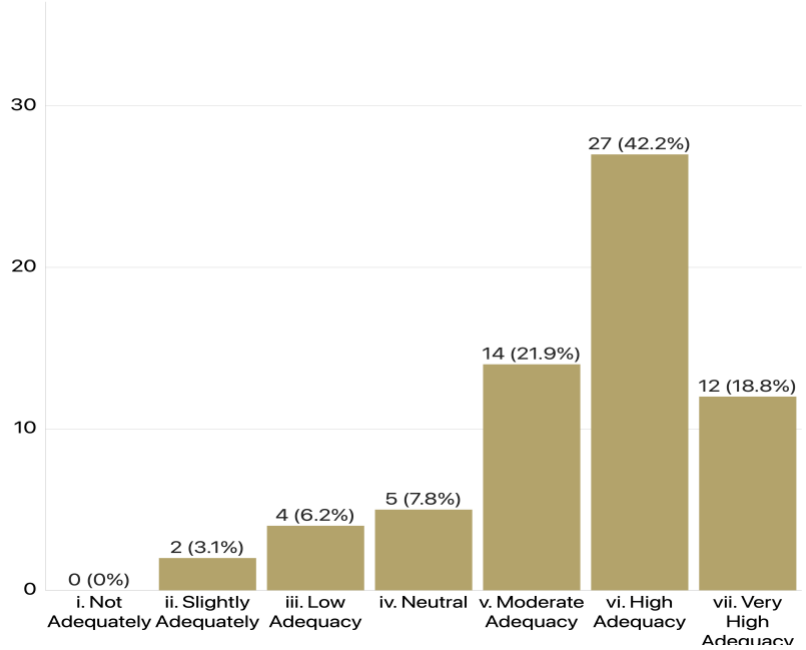

Figure 22: Segregation-related challenges promptly addressed, preventing long-term consequences on product quality and regulatory compliance

Segregation related challenges addressed to prevent consequences on product quality and regulatory compliance	**Number of Participants**	**Response Rate (%)**
Not Adequately	0	0%
Slightly Adequately	2	3.1%
Low Adequacy	4	6.2%
Neutral	5	7.8%
Moderate Adequacy	14	21.9%
High Adequacy	27	42.2%
Very High Adequacy	12	18.8%

Table 13: Segregation-related challenges promptly addressed, preventing long-term consequences on product quality and regulatory compliance

About 27 out of 64 (42.2%) participants positively responded for high adequacy that the challenges related to segregation were addressed to prevent consequences on product quality and regulatory compliance. Surprisingly, no participants responded to the response “not adequately”. 2 out of 64 (3.1%) participants responded for slight adequacy for challenges related to segregation. About 4 participants who responded to low adequacy was found to be 6.2%. Participants who responded neutrally were found to be 5 in number and the response rate was found to be 7.8%. 14 out of 64 participants responded to moderate adequacy with a response rate of 21.9%. 12 out of 64 participants responded to very high adequacy with a response rate of 18.8%.

In order to avoid long-term effects on product quality and regulatory compliance in pharmaceutical production, segregation-related issues must be addressed quickly and effectively. Manufacturers understand the need to mitigate segregation difficulties since failure to do so may result in variations in content consistency and perhaps compromise regulatory compliance. In order to quickly detect and address issues linked to segregation, industry practices place a strong emphasis on preventative measures and ongoing improvement. Companies are prepared to move quickly to take corrective and preventive measures should segregation issues emerge. To find the fundamental causes of segregation, root cause analysis is done, and then remedial action is taken to address the problems. These steps not only help to maintain long-term regulatory compliance but also avert immediate consequences on the quality of the product.

Question 12: How likely are you to recommend or implement strategies to improve segregation prevention in your manufacturing process?

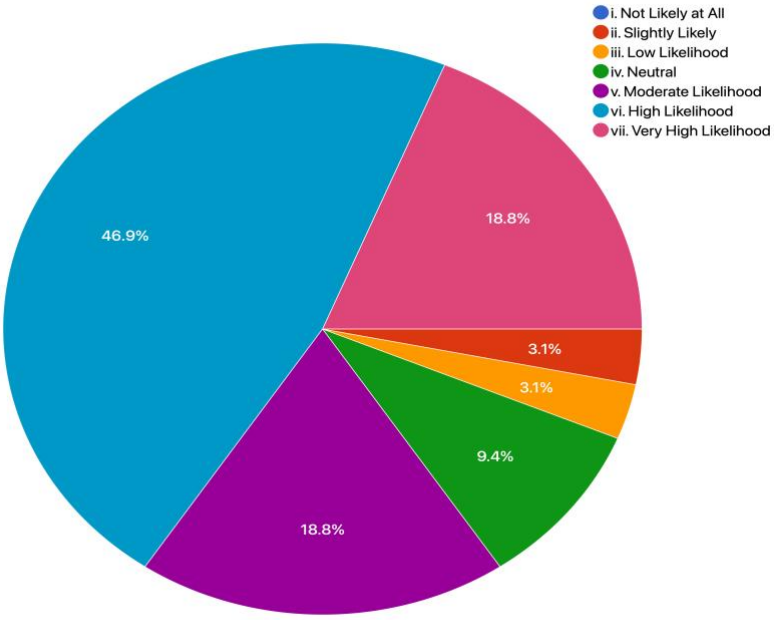

Figure 23: Implement strategies to improve segregation prevention in your manufacturing process

Implement strategies to improve segregation prevention in manufacturing process	Number of Participants	Response Rate (%)
Not Likely at All	0	0%
Slightly Likely	2	3.1%
Low Likelihood	2	3.1%
Neutral	6	9.4%
Moderate Likelihood	12	18.8%
High Likelihood	30	46.9%
Very High Likelihood	12	18.8%

Table 14: Implement strategies to improve segregation prevention in your manufacturing process

It was found that about 30(46.9%) out of 64 participants responded positively for implementing strategies to minimise segregation in the manufacturing process. No participants responded negatively to minimise segregation. 2(3.1%) out of 64 participants both responded to “slightly likely” and “low likelihood” in terms of implementing strategies to prevent segregation in the manufacturing unit. Number of participants whose response was neutral was found to be (6/9.4%). Participants openly expressed the response as moderate likelihood in terms of incorporating strategies to overcome segregation issues in pharmaceutical industries. The respondents who supported with very high likelihood were found to be 12 out of 64 and the response rate was found to be 18.8%.

Given the significant influence of segregation on product quality and regulatory compliance, there is a good chance that solutions to increase segregation prevention in a manufacturing process will be recommended or put into practice. Pharmaceutical companies have a strong motivation to improve their preventive tactics proactively, given the possible repercussions of segregation-related issues. The use of cutting-edge machinery, cutting-edge technology, and rigorous process controls is essential for reducing the chance of segregation during the manufacture of solid dose. Putting money into thorough training programmes for staff members guarantees that they are more knowledgeable of segregation prevention techniques, which promotes a culture of quality inside the company.

Question 13: How high of a priority should investment in segregation prevention be in your organization?

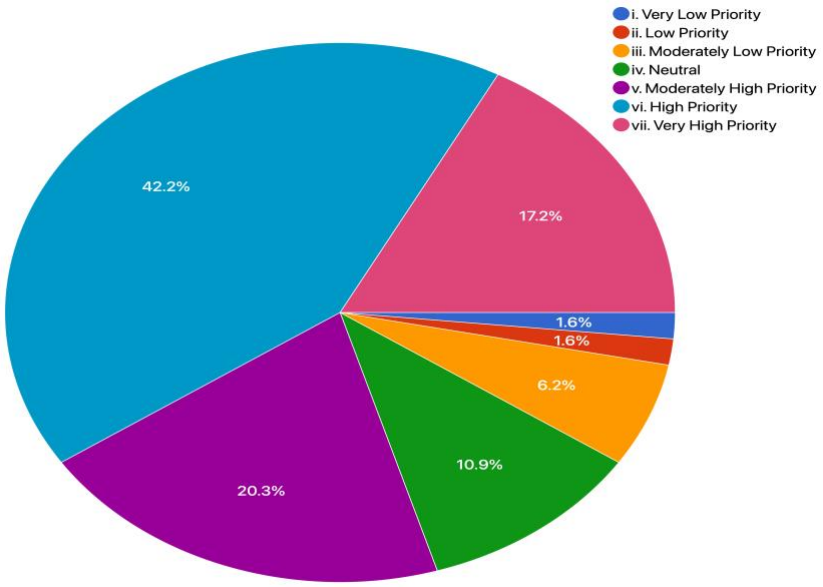

Figure 24: Investment in priority of segregation prevention in your organization

Investment in priority of segregation prevention in your organization	Number of Participants	Response Rate (%)
Very Low Priority	1	1.6%
Low Priority	1	1.6%
Moderately Low Priority	4	6.2%
Neutral	7	10.9%
Moderately High Priority	13	20.3%
High Priority	27	42.2%
Very High Priority	11	17.2%

Table 15: Investment in priority of segregation prevention in your organization

About 27(42.2%) out of 64 participants responded that it is a high priority that their respective organizations would prioritize investment in segregation prevention. Participants

that showed similar response rate was found to be 1.6% and their respective responses were found to be “very high priority” and “low priority” from the survey study. Participants who supported for moderately low priority had a response rate of 6.2%. Seven participants do not agree nor disagree to the idea of investing in priority of segregation prevention and the response rate was found to be 10.9%. Surprisingly, 11 participants responded positively for very high priority and the response rate was found to be 17.2%. Only 13 participants supported for moderately high priority and the response rate was found to be 20.3%. Thereby, the most responses were received for high priority in terms of investing measures to minimise or prevent segregation in manufacturing unit procedures.

Considering its critical role in guaranteeing regulatory compliance, product quality, and overall operational excellence, the organisation should place the greatest priority on investing in segregation prevention. Having acknowledged the significant influence that segregation has on the consistency of solid dosage forms, the company is dedicated to giving strong preventative measures first priority when allocating financial and strategic resources. Recognising that issues connected to segregation can have far-reaching effects, from variations in content consistency to possible non-compliance with regulations, serves to emphasise this commitment.

Question 14: To what extent does your organization provide support for initiatives aimed at preventing segregation in solid dosage manufacturing?

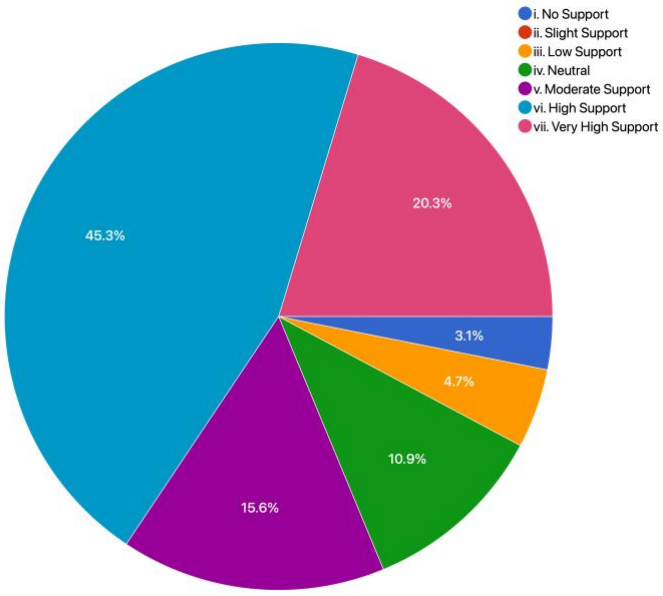

Figure 25: Initiatives aimed at preventing segregation in solid dosage manufacturing

Initiatives aimed at preventing segregation in solid dosage manufacturing	Number of Participants	Response Rate (%)
No Support	2	3.1%
Slight Support	0	0%
Low Support	3	4.7%
Neutral	7	10.9%
Moderate Support	10	15.6%
High Support	29	45.3%
Very High Support	13	20.3%

Table 16: Initiatives aimed at preventing segregation in solid dosage manufacturing

It is evident that 29 (45.3%) out of 64 participants believe that their respective organizations provide support for initiatives aimed at preventing segregation in solid dosage manufacturing. Two participants responded that the organization they work does not provide any support in terms of addressing segregation issues in the manufacturing field and the response rate was found to be 3.1%. Followed by it was found that no participants responded to getting slight support from their respective organizations in order to come up with strategies to minimise segregation. 3 out of the 64 participants also responded that they get low support from the company's end in terms of providing initiatives to prevent segregation in solid dose manufacturing. About 7 participants responded with a neutral response and the response rate was found to be 15.6%. Moderate support was received from 10 out of 64 participants and the response rate was found to be 15.6%. Only 13 participants responded with very high support with a response rate of 20.3%.

5. CONCLUSION

5.1. Outcome of the research study

This thesis aims to investigate the Northern Indian Pharmaceutical Industry and the progress made in the development of solid dosage forms with the goal of minimising segregation. These were the aims of the research:

- To what extent do issues associated with implementing segregation practices into role affect the productivity and operational procedures of solid dosage form production in Northern India's pharmaceutical industry.
- In what ways does the proper application of segregation techniques in the manufacturing of solid dosage forms provide solutions for pharmaceutical companies in Northern India in terms of personnel training and skill development.
- To investigate the current challenges that pharmaceutical industries, face in terms of segregation.
- To investigate any recent changes which lead to minimising segregation for an effective solid dosage manufacturing process.

Answering the research questions

1. **Issues associated with implementing segregation practices into role affect the productivity and operational procedures**

The objective of the proposed study is to investigate the complex link that exists between the difficulties in putting segregation methods into effect and how these challenges affect the production efficiency and operational processes of solid dosage forms in the pharmaceutical sector of Northern India. The degree to which these concerns affect productivity is a complex investigation that takes into account factors including manufacturing process efficiency, production schedule observance, and overall operational workflow. Complexities arising from segregation concerns, such the requirement for specialised equipment, facility adjustments, and strict protocols, have the ability to impede the efficient running of the manufacturing process. The success of segregation measures is also greatly influenced by elements like employee training and the incorporation of new technology. To optimise

operational procedures, strategies must take into account the interplay between these difficulties and their effects on production. In the pharmaceutical environment of Northern India, this research seeks to provide insights that can aid in the creation of targeted solutions that promote a balance between strict segregation regulations and the effective manufacturing of high-quality solid dosage forms.

It is evident that from the survey study (Question No. 6) 29 out of 64 participants positively responded in terms of effect of segregation on production timelines and delivery schedules. Surprisingly, no participants responded that there is no effect of segregation over productivity and operational procedures. However, 7 out of 64 participants responded with a neutral response for the above mentioned. Thereby, it is evident that majority of the participants believed that segregation does have an impact over productivity due to which strategies to overcome segregation are implemented in manufacturing procedures.

2. **Proper application of segregation techniques in the manufacturing of solid dosage forms provide solutions for pharmaceutical companies in Northern India in terms of personnel training and skill development.**

Northern Indian pharmaceutical manufacturers have significant hurdles when it comes to employee education and skill development regarding the efficient application of segregation techniques in the production of solid dosage forms. The necessity for workers with specialised knowledge and competence to carry out segregation measures is one of the main challenges. Ongoing training programmes are essential due to the dynamic nature of pharmaceutical production technology and strict regulatory requirements. However, there can be difficulties in getting hold of complete training modules, especially for smaller pharmaceutical organisations. In addition, employees must follow intricate segregation procedures and quickly adjust to evolving manufacturing processes due to the varied and dynamic nature of the solid dosage form production process. Uniform understanding and application of segregation measures might also be hampered by linguistic hurdles and differences in educational backgrounds among the workforces. As the industry adopts innovations like automated production and process analytical technologies, it is more important than ever to make sure that staff members are qualified to run and repair these systems. To overcome these obstacles, a deliberate emphasis on extensive training initiatives is required, possibly aided by partnerships with academic institutions and trade associations,

in order to provide pharmaceutical staff in Northern India with the necessary competencies for the efficient application of segregation procedures in the production of solid dosage forms. (Lakio *et al.*, 2017)

However, from the survey study conducted it is evident that the about 31(48.4%) out of 64 participants responded positive that their respective organizations provided adequate training to the employees for the prevention or minimising segregation in manufacturing operations. Surprisingly, only one participant strongly disagreed for the same. Thereby, it is clear that the majority of participants responded in favour stating that adequate training is provided in their respective pharmaceutical manufacturing operating units.

3. **Current challenges that pharmaceutical industries, face in terms of segregation**

The analysis of the segregation issues that the pharmaceutical industries are currently facing includes an in-depth investigation at important aspects of the manufacturing environment. The emphasis shifts to regulatory compliance, with an analysis of how pharmaceutical companies manage and adhere to changing regulatory frameworks pertaining to segregation practices. This paper explores the use of cutting-edge technology, examining the difficulties in implementing automation, process analytical technologies, and sophisticated equipment in the production of solid dosage forms. A review of the knowledge and skill gaps that already exist, along with the availability of specialised training programmes, make personnel training and skill development crucial considerations. Constraints related to infrastructure and facilities are assessed, and the costs and viability of upgrading current facilities to satisfy segregation regulations are investigated. This research takes into account the complexity posed by varying formulations and potencies as well as the effect that a varied product range has on segregation issues. Considerations related to the supply chain are examined, clarifying difficulties in upholding segregation criteria across the supply chain for pharmaceuticals. Requirements for segregation procedures that may be improved include operational efficiency, quality control, financial implications, and worldwide benchmarking. These factors all contribute to a thorough awareness of the difficulties faced by the pharmaceutical industry.

4. **Recent changes which lead to minimising segregation for an effective solid dosage manufacturing process**

Recent developments impacting the reduction of segregation in the efficient production of solid dosage forms are being examined, and the results show a technologically advanced and changing industrial environment. Notably, production process simplification and a decrease in the requirement for significant segregation have been made possible by the implementation of sophisticated manufacturing technologies, such as continuous manufacturing and real-time process monitoring. By enabling more exact control over production conditions, these technologies reduce the possibility of cross-contamination. The pharmaceutical sector has also been driven to review and improve their segregation procedures due to the increasing focus on quality risk management and the move towards a more comprehensive, risk-based regulatory approach. It's possible that contemporary regulatory frameworks take a sophisticated view of what is possible in terms of manufacturing today, allowing room for creative solutions that improve productivity and quality. A more educated and dynamic approach to segregation is also facilitated by industry-wide collaborative initiatives that strive to share best practices and expertise. In order to acquire a more efficient solid dosage production process with fewer segregation issues, pharmaceutical vendors have adopted several tactics and adjustments, which this inquiry aims to examine and evaluate.

5.1.1. Challenges faced during the implementation of strategies to minimise segregation in Indian Pharmaceutical industries.

Numerous constraints that affect the effectiveness of these initiatives impede the execution of remedies to reduce segregation in the Indian pharmaceutical industry. Some of the key challenges are:

i. **Diverse Product Range:** A vast range of products with different formulations, potencies, and manufacturing techniques are produced by the pharmaceutical sector. It can be difficult and resource-intensive to develop segregation techniques that accommodate this variability.
ii. **Outdated Infrastructure**: It's possible that many pharmaceutical plants in India still use outdated infrastructure that doesn't comply with contemporary segregation

regulations. Upgrading and retrofitting facilities to comply with modern standards comes with significant financial and practical difficulties.

iii. **Personnel Training and Awareness:** Ineffective implementation is caused by team employees' lack of knowledge and training on the most recent segregation techniques. Inconsistencies in following segregation procedures might result from a lack of thorough training programmes.

iv. **Economic repercussions:** There are major economic implications when segregation strategies are used. Pharmaceutical companies may face economic strain from expenses associated with technology adoption, facility upgrades, and continuing compliance activities.

v. **Complexity of the Global Supply Chain:** Complications arise when coordinating and guaranteeing uniform segregation standards throughout a global pharmaceutical supply chain. Encounters with outside vendors and varied sources provide difficulties for maintaining consistent compliance.

vi. **Dynamics of Regulatory Compliance:** It is a constant struggle to navigate the changing regulatory environment with its needs and expectations for compliance. Companies need to make sure they are adhering to changing standards and being informed about regulatory updates.

vii. **Coordination Challenges Across Production Stages:** It can be difficult to maintain consistent compliance with guidelines for segregation throughout the production process, particularly in large and intricate industrial operations.

5.1.2. Initiatives taken by the Indian pharmaceutical sector in Implementing strategies to overcome segregation in manufacturing of solid dosage forms.

In order to successfully execute techniques meant to overcome segregation issues related to the manufacture of solid dosage forms, the Indian pharmaceutical sector has launched a number of initiatives. The broad use of cutting-edge technologies like process analytical technology (PAT) and continuous production is one remarkable accomplishment. By enabling accurate control and real-time monitoring, these technologies improve segregation procedures and reduce the chance of cross-contamination. The pharmaceutical sector has also made large investments to update their production facilities in order to comply with the latest segregation regulations. Segregation protocols are adhered to by the workforce with the

support of skill development and extensive staff training programmes that have been put in place to raise awareness. The industry's cooperative activities, including as collaborations with research institutions and trade groups, have been crucial in exchanging segregation-related best practices and insights. Maintaining a proactive relationship with regulatory agencies guarantees adherence to changing policies and procedures. The pharmaceutical industry in India is committed to producing safe and high-quality solid dosage forms while facing segregation hurdles. This is further evidenced by the industry's continuous improvement activities, quality control systems, and adherence to global quality standards.

5.2. Concluding remarks and research constraints

In conclusion, the study of how segregation affects the development and production of solid dosage forms in the pharmaceutical industries of Northern India offers insightful information on a crucial and intricate feature of the pharmaceutical industry. The results highlight the various obstacles that the sector must overcome to effectively adopt segregation techniques. It also emphasises the significance of tailored approaches to tackle issues such as a wide range of products, outdated infrastructure, and limitations of employee training. The limits of the study must be acknowledged, despite the potential benefits of measures like the adoption of modern technology and partnerships with industry groups and regulatory agencies. These might include the extent to which the results can be applied outside of the particular sector and geographic context, possible biases in the self-reported data, and the dynamic nature of the pharmaceutical environment that can change after the research is completed. Notwithstanding these drawbacks, the study establishes a framework for further analysis and enhancement of pharmaceutical production segregation techniques, hence advancing the ongoing enhancement of industry standards in Northern India and elsewhere.

The notion that this research study was conducted in a short period with a limited number of participants is one of its limitations. Just 64 pharmaceutical experts who were employed by the various companies answered to the survey, despite 100 professionals receiving it. A small percentage of individuals denied to take part in the survey study as well. This is a primary cause of the comparatively low response rate. A significantly larger population must get the survey questionnaire in order to assess people's understanding of the idea in the Indian pharmaceutical industry.

In conclusion, I was able to draw the conclusion that the pharmaceutical industry's only goal is to determine how effectively their strategies contribute to minimising segregation, based on the responses of the employees that I collected through an online survey. The results of the survey indicate that the companies are focusing on their manufacturing operations efficiently, despite the employees' varied perspectives and insights regarding the impact of segregation in the production of solid dosage forms.

5.3. Recommendations for future research

Several important suggestions for future directions might be taken into consideration in order to further progress research on examining the impact of segregation in the manufacture of solid dosage forms in the pharmaceutical industry of Northern India. First and foremost, comprehensive research is required to address the practical implementation issues that pharmaceutical companies have when implementing segregation techniques, taking into account the subtleties of various manufacturing processes and facility sizes. In order to improve and optimise segregation processes, researchers should also investigate the integration of cutting-edge technologies like artificial intelligence and machine learning. Establishing a comprehensive knowledge of segregation practices through collaborative initiatives between academia, industry, and regulatory agencies is vital in order to provide standardised norms and best practices. Subsequent investigations may also explore the socio-economic consequences of segregation tactics, assessing their effects on the labour force, nearby communities, and the wider pharmaceutical industry. Last but not least, a study of the possible effects of world occurrences, like the COVID-19 pandemic, on supply chain resilience and segregation techniques would offer useful information for modifying production procedures in the face of unanticipated difficulties. All things considered, segregation practices in the pharmaceutical manufacturing industry in Northern India will advance considerably with an all-encompassing and interdisciplinary approach that takes into account technological innovations, collaborative frameworks, socio-economic considerations, and adaptability to global dynamics.

6. REFERENCE

Baxter, T. and Prescott, J. (2009) *Chapter 28 - Process Development, Optimization, and Scale-Up: Powder Handling and Segregation Concerns*. *ScienceDirect*. Available at: https://www.sciencedirect.com/science/article/abs/pii/B978044453242800028X (Accessed: 6 January 2024).

Carson, J.W. (1988) 'Overcoming Particle Segregation in the Pharmaceutical and Cosmetics Industries'. *Drug Development and Industrial Pharmacy*, 14(18), pp. 2749–2758. DOI: https://doi.org/10.3109/03639048809152046.

Deng, T. *et al.* (2021) 'Correlations between Segregation Intensity and Material Properties such as Particle Sizes and Adhesions and Novel Methods for Assessment'. *Powder Technology*, 387, pp. 215–226. DOI: https://doi.org/10.1016/j.powtec.2021.04.023.

Deng, T. *et al.* (2010) 'Investigations on Air Induced Segregation of Pharmaceutical Powders and Effect of Material Flow Functions'. *Powder Technology*, 203(2), pp. 354–358. DOI: https://doi.org/10.1016/j.powtec.2010.05.028.

Devriendt, L., Cendrine Gatumel. and Henri Berthiaux. (2013) 'Experimental Evidence of Mixture Segregation by Particle Size Distribution'. *Particulate Science and Technology*, 31(6), pp. 653–657. DOI: https://doi.org/10.1080/02726351.2013.832447.

He, X. *et al.* (2013) 'Assessing Powder Segregation Potential by near Infrared (NIR) Spectroscopy and Correlating Segregation Tendency to Tabletting Performance'. *Powder Technology*, 236, pp. 85–99. DOI: https://doi.org/10.1016/j.powtec.2012.05.021.

Hildebrandt, C. *et al.* (2018) 'Simulation of Particle Size Segregation in a Pharmaceutical Tablet Press Lab-Scale Gravity Feeder'. *Advanced Powder Technology*, 29(3), pp. 765–780. DOI: https://doi.org/10.1016/j.apt.2017.12.019.

Jain, A., Metzger, M. and Glasser, B.J. (2013) 'Effect of Particle Size Distribution on Segregation in Vibrated Systems'. *Powder Technology*, 237, pp. 543–553. DOI: https://doi.org/10.1016/j.powtec.2012.12.044.

Jaklič, M. *et al.* (2015) 'Particle Size-Based Segregation of Pharmaceutical Powders in a Vertical Chute with a Closed Bottom: An Experimental Evaluation'. *Powder Technology*, 278, pp. 171–180. DOI: https://doi.org/10.1016/j.powtec.2015.03.021.

Jakubowska, E. and Ciepluch, N. (2021) ‘Blend Segregation in Tablets Manufacturing and Its Effect on Drug Content Uniformity—a Review’. *Pharmaceutics*, 13(11), p. 1909. DOI: https://doi.org/10.3390/pharmaceutics13111909.

Jivraj, M., Martini, L.G. and Thomson, C.M. (2000) ‘An Overview of the Different Excipients Useful for the Direct Compression of Tablets’. *Pharmaceutical Science & Technology Today*, 3(2), pp. 58–63. DOI: https://doi.org/10.1016/s1461-5347(99)00237-0.

Lakio, S. *et al.* (2017) ‘Provoking an End-To-End Continuous Direct Compression Line with Raw Materials Prone to Segregation’. *European Journal of Pharmaceutical Sciences*, 109, pp. 514–524. DOI: https://doi.org/10.1016/j.ejps.2017.09.018.

Melnikovas, A. (2018) *Towards an Explicit Research Methodology: Adapting Research Onion Model for Futures Studies*.

Nakamura, S. *et al.* (2019) ‘Utility of Microcrystalline Cellulose for Improving Drug Content Uniformity in Tablet Manufacturing Using Direct Powder Compression’. *AAPS PharmSciTech*, 20(4). DOI: https://doi.org/10.1208/s12249-019-1365-4.

Oka, S. *et al.* (2017) ‘Analysis of the Origins of Content Non-Uniformity in High-Shear Wet Granulation’. *International Journal of Pharmaceutics*, 528(1-2), pp. 578–585. DOI: https://doi.org/10.1016/j.ijpharm.2017.06.034.

Oka, S. *et al.* (2017) ‘Diminished Segregation in Continuous Powder Mixing’. *Powder Technology*, 309, pp. 79–88. DOI: https://doi.org/10.1016/j.powtec.2016.11.038.

Pernenkil, L. (2008) *Continuous Blending of Dry Pharmaceutical Powders*. *dspace.mit.edu*. Available at: https://dspace.mit.edu/handle/1721.1/42945 (Accessed: 6 January 2024).

Römerová, S., Dammer, O. and Zámostný, P. (2021) ‘Streamlining of the Powder Mixing Process Based on a Segregation Test’. *AAPS PharmSciTech*, 22(5). DOI: https://doi.org/10.1208/s12249-021-02073-z.

Sanjay Kumar Verma., Yogi, J. and Anand, A. (2021) ‘Experimental Investigation of Segregation for Nonspherical Particles in a Fluidized Bed Solids Mixer’. *Industrial & Engineering Chemistry Research*, 60(6), pp. 2642–2651. DOI: https://doi.org/10.1021/acs.iecr.0c04683.

Sever, N.E. *et al.* (2009) *Chapter 35 - Process Analytical Technology in Solid Dosage Development and Manufacturing*. *ScienceDirect*. Available at: https://www.sciencedirect.com/science/article/abs/pii/B9780444532428000357 (Accessed: 6 January 2024).

Shah, K.R. *et al.* (2007) ‘Assessment of Segregation Potential of Powder Blends’. *Pharmaceutical Development and Technology*, 12(5), pp. 457–462. DOI: https://doi.org/10.1080/10837450701556834.

Shaikh, R. (2018) ‘The Development of a Pharmaceutical Oral Solid Dosage Forms’. *Computer Aided Chemical Engineering*, 41, pp. 27–65. DOI: https://doi.org/10.1016/B978-0-444-63963-9.00002-6.

TANG, P. and PURI, V.M. (2004) ‘Methods for Minimizing Segregation: A Review’. *Particulate Science and Technology*, 22(4), pp. 321–337. DOI: https://doi.org/10.1080/02726350490501420.

Teżyk, M. *et al.* (2015) ‘Recent Progress in Continuous and Semi-Continuous Processing of Solid Oral Dosage Forms: A Review’. *Drug Development and Industrial Pharmacy*, 42(8), pp. 1195–1214. DOI: https://doi.org/10.3109/03639045.2015.1122607.

Tolba, M.M. and Salim, M.M. (2021) ‘Inclusive Study for Segregation of Two Commonly Used Anticancer Drugs with Tramadol: Applying a Green Fluorimetric Strategy to Pharmaceutical Dosage Forms and Human Plasma’. *Microchemical Journal*, 162, p. 105859. DOI: https://doi.org/10.1016/j.microc.2020.105859.

Wu, E.L. *et al.* (2021) ‘High-Throughput Blend Segregation Evaluation Using Automated Powder Dispensing Technology’. *European Journal of Pharmaceutical Sciences*, 159, p. 105702. DOI: https://doi.org/10.1016/j.ejps.2021.105702.

APPENDIX

Online Survey Questionnaire

Title of the Study: **Investigating the effect of segregation in the manufacturing of solid dosage forms in pharmaceutical industries in Northern India**
Principal Investigator: **Hridya Uday**
Affiliation: **Griffith College Dublin**

Introduction:

I, the undersigned, understand that I am being invited to participate in a research study titled " Investigating the effect of segregation in the manufacturing of solid dosage forms in pharmaceutical industries in India." The purpose of this study is to gather information about the perceptions and experiences of individuals working in the pharmaceutical manufacturing industry regarding the effects of segregation on solid dosage manufacturing.

Study Procedures:

If I agree to participate, I will be asked to complete a questionnaire comprising 14 questions. The questionnaire includes Likert scale questions and open-ended questions about your experiences and opinions related to segregation in solid dosage manufacturing.

Risks and Benefits:
There are minimal risks associated with participating in this study. The information provided will be kept confidential and used for research purposes only. No personally identifiable information will be disclosed in any reports or publications resulting from this research. Participation in this study is voluntary. There are no direct benefits to you for participating in this study; however, the information gathered will contribute to the understanding of the impact of segregation in solid dosage manufacturing.

Confidentiality:
All information provided in the questionnaire will be kept confidential. Your responses will be anonymized, and no personally identifiable information will be disclosed. The data collected will be stored securely and will only be accessible to the researchers involved in this study.

Voluntary Participation:
My participation in this study is entirely voluntary. I understand that I have the right to withdraw from the study at any time without penalty or loss of benefits to which I am otherwise entitled. If I choose to withdraw, I may do so by exiting the survey before submitting my responses.

Contact Information:
If I have any questions or concerns about this study, I may contact the Principal Investigator, Hridya Uday, at [hridya.uday@student.griffith.ie]. If I have any concerns about my rights as a participant, I may contact the Institutional Review Board (IRB). (Griffith College, 2023)

Consent:
I have read the above information, and I voluntarily agree to participate in this study. I understand the purpose of the study, the procedures involved, and the voluntary nature of my participation.
Participant's Name: _____
Participant's Signature: _____
Date: _____

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* Indicates required question

1. Please specify your position or role in the pharmaceutical manufacturing industry:
*

- ☐ i. Production Supervisor
- ☐ ii. Quality Control Analyst
- ☐ iii. Research and Development Scientist
- ☐ iv. Compliance Officer
- ☐ v. Quality Assurance Manager
- ☐ vi. Supply Chain Manager
- ☐ vii. Other (please specify): _____

2. How many years of experience do you have in solid dosage manufacturing within the pharmaceutical industry?
*

- ☐ i. Less than 1 year
- ☐ ii. 1-2 years
- ☐ iii. 3-5 years
- ☐ iv. 6-10 years
- ☐ v. 11-15 years
- ☐ vi. 16-20 years
- ☐ vii. More than 20 years

3. Please rate the overall impact of segregation on solid dosage manufacturing in your opinion.
*

- ☐ i. No Impact
- ☐ ii. Slight Impact
- ☐ iii. Low Impact
- ☐ iv. Neutral
- ☐ v. Moderate Impact

- ☐ vi. High Impact
- ☐ vii. Very High Impact

4. To what extent do you believe that employees are adequately trained and aware of segregation issues in the manufacturing process?
*

- ☐ i. Strongly Disagree
- ☐ ii. Disagree
- ☐ iii. Somewhat Disagree
- ☐ iv. Neutral
- ☐ v. Somewhat Agree
- ☐ vi. Agree
- ☐ vii. Strongly Agree

5. How do you perceive the impact of segregation on the overall efficiency of solid dosage manufacturing?
*

- ☐ i. No Impact
- ☐ ii. Slight Impact
- ☐ iii. Low Impact
- ☐ iv. Neutral
- ☐ v. Moderate Impact
- ☐ vi. High Impact
- ☐ vii. Very High Impact

6. To what extent does segregation influence production timelines and delivery schedules?
*

- ☐ i. Not Influential
- ☐ ii. Slightly Influential
- ☐ iii. Low Influence
- ☐ iv. Neutral
- ☐ v. Moderate Influence
- ☐ vi. High Influence
- ☐ vii. Very High Influence

7. How effective are the existing quality control measures in detecting and addressing segregation issues?
*

- ☐ i. Ineffective
- ☐ ii. Slightly Effective
- ☐ iii. Low Effectiveness
- ☐ iv. Neutral
- ☐ v. Moderate Effectiveness
- ☐ vi. High Effectiveness
- ☐ vii. Very High Effectiveness

8. To what extent does segregation affect the overall cost of manufacturing solid dosage forms?

*

- ☐ i. No Impact
- ☐ ii. Slight Impact
- ☐ iii. Low Impact
- ☐ iv. Neutral
- ☐ v. Moderate Impact
- ☐ vi. High Impact
- ☐ vii. Very High Impact

9. How does segregation influence the overall product yield in solid dosage manufacturing?

*

- ☐ i. No Influence
- ☐ ii. Slight Influence
- ☐ iii. Low Influence
- ☐ iv. Neutral
- ☐ v. Moderate Influence
- ☐ vi. High Influence
- ☐ vii. Very High Influence

10. How often does segregation lead to deviations or non-compliance with regulatory requirements?

*

- ☐ i. Rarely
- ☐ ii. Occasionally
- ☐ iii. Infrequently
- ☐ iv. Neutral
- ☐ v. Frequently
- ☐ vi. Very Frequently
- ☐ vii. Always

11. To what extent are segregation-related challenges promptly addressed, preventing long-term consequences on product quality and regulatory compliance?

*

- ☐ i. Not Adequately
- ☐ ii. Slightly Adequately
- ☐ iii. Low Adequacy
- ☐ iv. Neutral
- ☐ v. Moderate Adequacy
- ☐ vi. High Adequacy
- ☐ vii. Very High Adequacy

12. How likely are you to recommend or implement strategies to improve segregation prevention in your manufacturing process?

*

- ☐ i. Not Likely at All
- ☐ ii. Slightly Likely
- ☐ iii. Low Likelihood
- ☐ iv. Neutral
- ☐ v. Moderate Likelihood
- ☐ vi. High Likelihood
- ☐ vii. Very High Likelihood

13. How high of a priority should investment in segregation prevention be in your organization?

*

- ☐ i. Very Low Priority
- ☐ ii. Low Priority
- ☐ iii. Moderately Low Priority
- ☐ iv. Neutral
- ☐ v. Moderately High Priority
- ☐ vi. High Priority
- ☐ vii. Very High Priority

14. To what extent does your organization provide support for initiatives aimed at preventing segregation in solid dosage manufacturing?

*

- ☐ i. No Support
- ☐ ii. Slight Support
- ☐ iii. Low Support
- ☐ iv. Neutral
- ☐ v. Moderate Support
- ☐ vi. High Support
- ☐ vii. Very High Support