RESEARCH PAPER

From pharmaceutical ingredients to drug delivery - Impact of flow, uniformity and contamination on product quality of solid dosage forms - A critical Review

Ravindra T. Bhosale[1]*, Sandip H. Gharat[2], Yogesh S. Mahajan[1]

[1]Department of Chemical Engineering, Dr. Babasaheb Ambedkar Technological University Lonere, Raigad, Maharashtra, India-402103

[2]Department of Chemical Engineering, Shroff S.R. Rotary Institute of Chemical Technology, UPL University of Sustainable Technology, Ankleshwar, Gujarat, India-393001

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ABSTRACT

Oral solid dosage form is known as gold standard for drug delivery system. These are available in different forms: tablets, capsules, granules, etc. This is crucial medication system due to its stability, patient compliance and cost effectiveness. Transformation of active pharmaceutical ingredients to oral solid dosage form needs rigorous and precise control over different manufacturing stages. This review highlights the critical parameters affecting performance and product quality consisting of powder flowability, content and mass uniformity, elimination of impurities and mitigation of contamination. Due to erratic flow, clogging is a common challenge in powder processing equipment and storage systems. This review examines the flow dynamics, clogging, segregation, impurities and contamination challenges from manufacturing active pharmaceutical ingredients to final solid dosage form. Recent advancement in mitigation techniques including particle engineering, excipient optimization, continuous manufacturing and Quality by Design (QbD) approaches are discussed. This helps to enhance process robustness and improve product quality. Simulation techniques, automation, Internet of Things (IoT), and artificial intelligence driven monitoring application are reviewed to control powder processing. This review discussed an integrated perspective on various challenges across the product lifecycle from active pharmaceutical ingredient manufacturing to drug delivery. This helps to provide future direction to enhance manufacturing efficiency, therapeutic reliability and regulatory compliances.

Keywords: Granules, solid dosage form, quality by design, clogging, segregation

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1. INTRODUCTION

Oral Solid dosages (OSD) are basically formulation of active pharmaceutical ingredients, which can be taken through mouth. Its formulation is simply converting drug molecules into a stable solid form. It comes in different forms such as tablets, capsules, granules, cachets, dropping pills and films or powders [1]. OSD are swallowed through mouth and designed to dissolve in the gastrointestinal tract, to allow the systematic delivery of API in the body. OSD accounts for approximately 70 % of the pharmaceutical requirement. OSD is widely used due to its physical, chemical and biological stability than liquid. Most active pharmaceutical ingredient (APIs) are solid and comparatively cost effective to make them in OSD form. It is convenient for packing and transporting. As oral administration is safer than other routes, OSD are always preferred [2].

To develop effective drug delivery, understanding the uniqueness of OSD forms is subject of concern. OSDs have distinct characteristics like efficient manufacturing, precise dosing, shelf stability, convenient administration and patient compliance. It is important to consider the physiochemical properties, distribution of ingredients and release of dosage form [3]. Careful attention and consideration needed for the specific therapeutic need of the patient to choose specific OSD. Compared to liquids or semi solids, solid formulation does not require refrigeration and are less prone to spoilage. Solid allow accurate dosing and consistent drug content. This is very

*Author for Correspondence: Ravindra T. Bhosale, Email: ravindra.bhosale77@gmail.com

crucial for effective treatment. Hence OSD form is always chosen form [4].

Evaluation of parameters such as density, porosity, moisture, content, friability, and flow properties is carried out. This review discusses fundamental mechanism to govern flow dynamics, segregation mechanism, and clogging behaviour. It also discusses impacts on performance of manufacturing and efficiency of drug delivery. It also directs rheology and critical quality attributes influencing blend uniformity, dissolution, stability, bioavailability and compressibility [5].

It is further categorized as bulk powder, cachet (Divided powder) and granules. Also specialized solids are designed as Lozenges and troches, suppositories and implants. Lozenges and troches are solids having disc shaped preparations to dissolve slowly in the mouth. Suppositories are the solids intended to insert in the cavities of body where it is dissolved to release the drug delivery. Implants are sterile solid devices placed under skin to release over extended period [6].

This review discusses potential challenges, and future perspectives related to storage and handling of powder. Gaps in the current literature are highlighted, suggesting areas for further development [7]. Recommendations are being made to guide future developments in this area, particularly in automation, Internet of Things (IoT), and artificial intelligence [8]. This review addresses new computational and predictive tools and provides roadmap from traditional predictive quality by Design (QbD) framework. This article addresses the challenges related to handling of powders and granules, providing insight into the factors affecting drug delivery systems [9]. The article updates the new technologies in simulation, automation, Internet of Things (IoT) and artificial intelligence (AI). This article also discusses powder flow techniques to improve flow techniques to improve flowability to enhance plant output and minimize product quality. This review article provides fundamental, descriptive knowledge to updated technologies. This article evaluates the macro-rheological aspect and discussed the particle engineering including particle size segregation, electrostatic sticking and mechanism of dose variation [10].

1.1 Types of Oral Solid Dosages:

1.1.1 Powder:

Powders consist of finely divided i.e. agglomerated drug particles. This can be used as oral and topical drug delivery. These are finely divided solids and used as precursor for other dosage forms. Powders are more prone to segregation leading to inconsistent uniformity of active pharmaceutical ingredients [11].

1.1.2 Granules:

Granules comprise of APIs and excipients. Granules are categorized as soluble granules, effervescent granules, suspending granules, enteric granules, sustained released granules and controlled release granules. Granules are preferred due to low dust formation, tends to agglomerate and hygroscopicity. Granules offer enhanced flow properties and compressibility. Its large particle size reduces dust generation [12].

1.1.3 Tablets:

Tablet is most prevalent form, having very diverse range of applications These are classified as buccal and sublingual tablets, chewable tablets and effervescent tablets. Tables are manufactured by compressing the mixture of API and excipients involving processes such as blending of API with excipients, granulation drying, sieving and compression. Tablets are formulated based on application of therapeutic indication and physicochemical properties depending on the patient [13].

Buccal tablets and sublingual tablets are used by dissolving in the mouth where rapid onset action is needed. Both tablets allow API to absorb directly in the blood stream, by passing the digestive system. Buccal tablets are designed to dissolve between cheek and gum. Sublingual tablets are placed under the tongue. These tablets are helpful, where drugs are destroyed by stomach acid or difficult to absorb through gut. Effervescent tablets consist of ingredients that, when immersed in water, releases carbon dioxide. This creates a solution which is easier for swallowing and easy to absorb. Chewable tablets are used for patients having difficulty in swallowing the compressed tablet. This allows the API to release and absorb in the bloodstream through the lining of the mouth. These tablets have comparable efficacy to other forms. Table 1 highlights the key difference between different forms [14-15].

Table 1: Key Difference Between Powder, Granules and tablets [11-15]

Application	Powder	Granules	Tablets
Nature	Fine particles	Small agglomerates	Compressed solid
Absorption rate	Fast	Moderate	Slow
Flowability	Poor	Good	Excellent
Surface area per unit volume	Large	Less than powder	Lowest
Compressibility	Very low	Better than powder	High
Dissolution rate	Fast	Moderate	Slow
Manufacturing	Simple processing	Moderate	Complex
Patient convenience	Poor	Good	Excellent
Stability	Variable due to Prone to moisture	More stable than powder	Very stable due to coating
Application	bulk formulation and suspension	controlled release formulation	Common in OSD for precise dosing

1.1.4 Capsules:

Capsules are oral drug delivery system which consist of shell made up of gelatine (hard capsules) and polymer or vegetable oil material (soft capsule). Capsules are formulated by using shell filled with active pharmaceutical ingredient (API) and excipient (binders, fillers and coatings) in powder or granule form. Both have unique merits and demerits based on drug formulation and drug delivery methods. Capsules are manufactured by using granulation, and coating processes. Capsules are also used

for modified released formulation such as enteric coated capsules. These capsules are designed to dissolve in the small intestine instead of stomach [16].

2. GRANULATIONS

Granulation involves the addition of liquid binder to the powder to from granules. These are then processed by drying, sieving and compression. Granulation can be classified as wet granulation and dry granulation. Excipients commonly used for granules consist of diluents, binders and disintegrant. Diluents are starch, lactose, sucrose and dextrin. It is a key process in the formulation to improve flow, compressibility and uniformity. Follwings are the various types of granulation processes [17].

2.1 Wet Granulation:

In wet granulation, fine powder (API) is agglomerated by adding liquid binder(excipients). Kneading, high shear granulators are used for agglomeration. This liquid binder creates solid bridges between fine particles. This wet mass is then dried in fluidized bed dryer to produce stable granule. If required sieving is done to achieve desired granule size. High-shear granulator, Fluidized bed granulator and Planetary mixer are used as granulators. It produces uniform granules and reduces segregation of fine powders. It improves tablet compressibility and content uniformity. This are used for tablets, capsules, modified-release formulations [18].

2.2 Dry Granulation:

In dry granulation, powder is compacted under pressure to form slugs or ribbons. It is then milled into granules. Liquid binder is not used in dry granulation. It comprises of blending, compaction, milling into granules and sieving to achieve desired size of granules. Roller compactor, Slugging press and Milling machines are used for dry granulation. This technique is mostly used for moisture-sensitive APIs. It does not require drying; hence it is more energy efficient. This process produces granules with good flow and compressibility. This process is especially used for moisture-sensitive drugs, effervescent tablets, some controlled-release tablets [19].

2.3 Fluidized Bed Granulation:

Powder is fluidized in an air stream, and binder solution is sprayed inside the chamber to form granules as droplets coat particles. This process involves fluidization of powder, atomized binder spray, agglomeration under controlled temperature and airflow and drying. It is used where uniform granule size is required. It provides simultaneous granulation and drying. It has good control over moisture content and is suitable for heat-sensitive active pharmaceutical ingredient. It is used for Immediate-release tablets, multi-particulate dosage forms and orally disintegrating tablets [20].

2.4 Spray Granulation:

Liquid solution is sprayed into a hot drying chamber. Granules are formed by evaporation of solvent. It produces highly uniform spherical granules. This is suitable for thermosensitive materials. It is used for inhalable powders, nanomedicine precursors and orally disintegrating and effervescent formulations [21].

2.5 Melt Granulation:

In melt granulation, a meltable binder is used instead of a solvent. Powder particles stick together as the binder solidifies. This process involves blend powder with molten binder, agglomeration under low shear, cooling and solidification and sieving to desired granule size. It uses high-shear mixer with heating and fluidized bed with heated air. It is Solvent-free and good for moisture-sensitive APIs. It is used to produces coated or modified-release granules. This are used for controlled-release tablets and taste-masked formulations [22].

2.6 Extrusion Spheronization :

Powder is extruded into cylindrical strands and then spheronized into pellets. This process involves powder blending with binder and excipients, extrusion through die to form rods, spheronization using friction plate to form spheres and drying and optional coating. It uses extruder, spheronizer and fluidized bed dryer. It is used to produces uniform spherical pellets. It is used for controlled-release or modified release multi-particulate systems, and it is beneficial for easy coating and reduced dose variability for Pellet-filled capsules. Table 2 provides the detailed comparison of various granulation techniques [23].

Table 2: Comparison of Granulation Techniques [17-23]

Type	Binder / Liquid	Heat Requirement	Advantages	Applications
Wet Granulation	Liquid binder	Moderate	Uniform, compressible granules	Tablets, capsules
Dry Granulation	None	Low	Moisture-sensitive, energy-efficient	Effervescent tablets, sensitive APIs
Fluidized Bed	Binder spray	Low to moderate	Uniform size, simultaneous drying	Multi-particulates, ODTs
Spray Granulation	API solution/suspension	High	Spherical granules, controlled particle size	Inhalable, nanomedicine
Melt Granulation	Meltable binder	Low	Solvent-free, moisture-sensitive	Controlled-release, taste-masked
Extrusion-Spheronization	Binder	Moderate	Uniform pellets, controlled release	Pellet capsules, multi-particulates

3 DRUG DELIVERY SYSTEMS (DDS)

Drug delivery is the process of administrating the medicine inside the body in which the pharmaceutical compound reaches at desired location with required concentration, duration and rate to achieve the desired therapeutic effect safely and effectively. This improves bioavailability,

controls the release rate of the drug, reduces side effect and toxicity.

Powder flow, segregation, clogging and contamination may affect dose uniformity, dissolution kinetic stability, drug delivery performance and therapeutic efficacy. Drug delivery can be routed through oral, injectable, topical, pulmonary, transdermal, nasal etc. Oral administration is most popular method. This oral delivery is more sustained and controlled delivery due to ease of administration. It also enhances immunity [24].

Biopharmaceuticals in aqueous form are often used in drug delivery systems. It's prone to physical as well as chemical degradation [25].

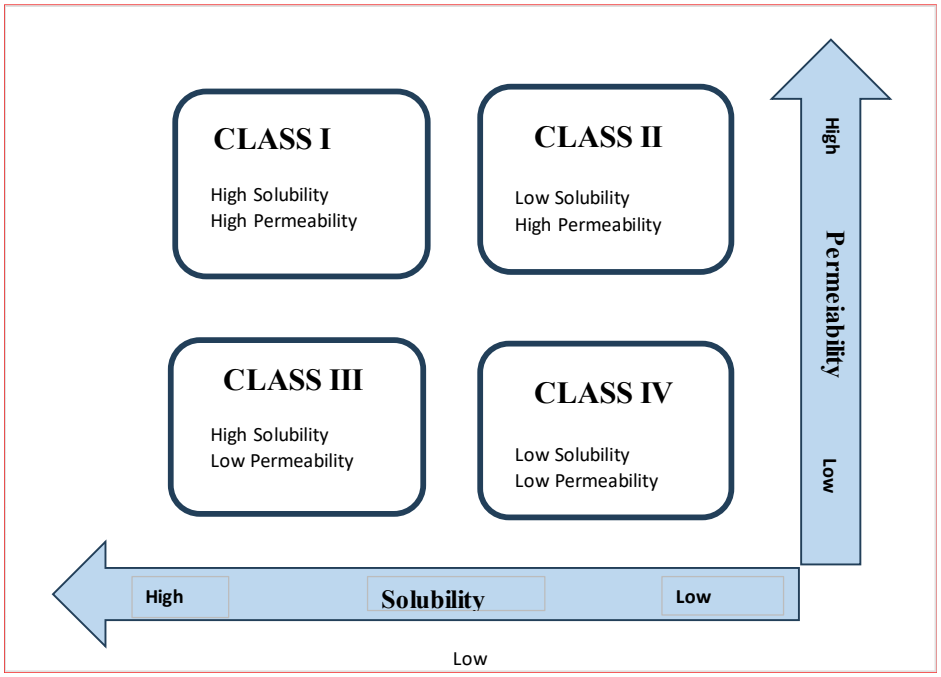

Figure 1: biopharmaceuticals classification system [25].

Various techniques are used to convert it from aqueous to solid dosage form. Freeze- drying, spray-drying and spray-freeze-drying are most used techniques. Supercritical fluids (supercritical carbon dioxide) are a sustainable alternative for common techniques in the production of solid biopharmaceutical dosage form. These are used as a solvent, co-solvent, antisolvent or co-solute [1]. Though OSD has advantages, it may effect on bioavailability due to poor water solubility, permeability and dissolution rate. Improving the same is a major challenge.

Oral solid dosages are absorbed in body by four different ways: assisted transport, transcellular, paracellular and carrier mediated transcellular. The biopharmaceuticals classification system (BCS) is categorized into four classes as shown in figure 1. BCS class I drug are suitable for oral administration due to high permeability and solubility. Whereas other classes are not suitable for oral delivery due to low permeability and solubility or either or [25].

3.1 Regulatory Compliances in Drug delivery system:

Due to stringent regulatory compliance, pharmaceutical industries are focusing on continuous manufacturing and automation with data-driven manufacturing. Storage system is crucial due to sensitivity towards temperature, humidity, impurities and contamination. Smart silos are playing a crucial role for continuous manufacturing enabling real-time sensing, intelligent processing and decision-making. Smart silos with IoT integrate sensor network, analytics and cloud computing. This ensures real time monitoring and control of manufacturing [26].

According to ICH Q7 guidelines, APIs are highly sensitive towards quality, stability and purity, it needs controlled storage conditions to prevent contamination. Also, traceability is needed to ensure the quality of product. Traditional storage system has lack of real time monitoring, degradation due to temperature and moisture variation, contamination risk. To overcome these issues intelligent storage systems (smart silos) are used in pharmaceutical industries. In pharmaceutical application, silo acts as dynamic unit operation rather than passive equipment, as it influences on flow, uniformity and purity of the API. Silo geometry, discharge mechanism and properties of particles govern the behaviour of material inside silo [27].

4 FLOW DYNAMICS OF ORAL SOLID DOSAGE IN SILOS

Depending on silo geometry, flow patterns are characterised as mass flow, funnel flow and expanded flow. As shown in Figure 2, in mass flow, entire material is in continuous motion while discharging. It slides along the wall smoothly following first in first out (FIFO) sequence. This is important for uniform residence time to ensure prevention of degradation of product. But if the wall friction is high and having too shallow wall, the flow

creates last-in first out (LIFO) profile creating stagnant zone along the walls [28].

Hence flow regime, inside silo influences on either uniform flow or segregation.

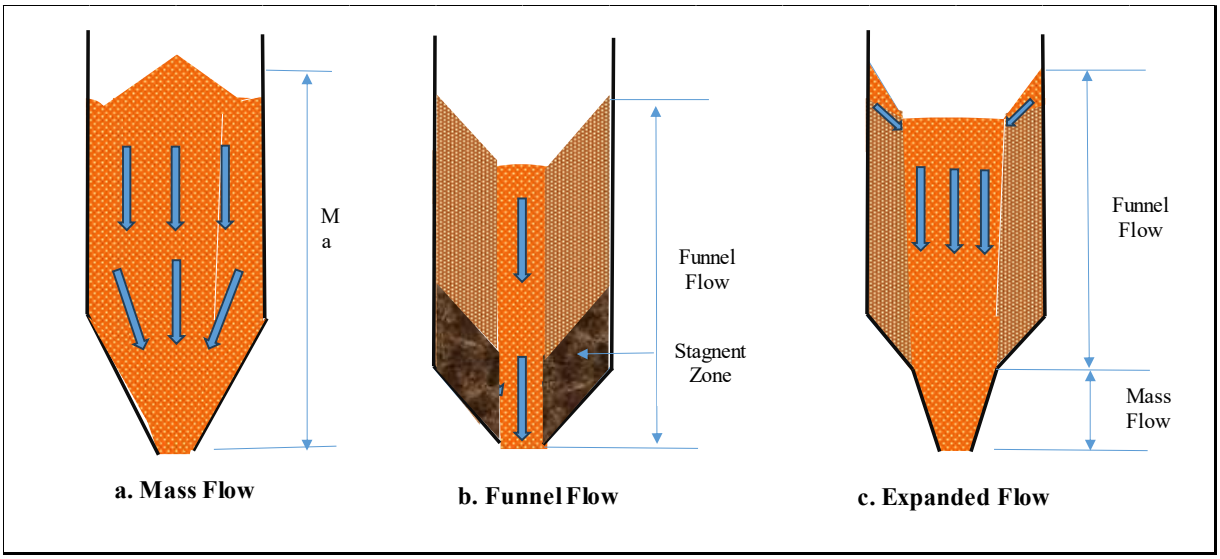

Figure 2: Modes of Flow a. Mass Flow, b. Funnel Flow, C. Expanded Flow. [28]

Due to funnel flow profile, Sifting segregation causes fine particles to move from the centre, while coarse particles stay on the side stagnant zone. This disturbs the content uniformity, dosage variation between batch cycle. This can be corrected by providing mass flow, as entire cross section flows simultaneously resulting effective remixing of horizontal segregation at the discharge outlet. Due to physical boundary conditions inside the silo, API's alters the physical and chemical properties resulting in degradation. generation of impurities and contamination of products. In funnel flow, powder sticks in stagnant zone for prolonged time [29]. Due to moisture or temperature variation caking is formed, leading to agglomerate impurities. Due to roughness of the inside surface of the wall, cohesive API particles stick to the wall. This layers then degrade over the time. These leads to severe cross contamination in upcoming batches.

Transition of flow between mass and funnel flow generate pressure fluctuation at the outlet resulting in stochastic clogging. This results in variation in tablet density [30].

Manufacturing solid dosage forms involves various powder processing stages. Effective of these operations influence on product quality, safety and therapeutic performance. Challenges related to flow, clogging, segregation and contamination are major concern from manufacturing of APIs to final drug delivery. The variation in size and shape of particles, density, surface properties and moisture results in inconsistent dosing, content uniformity, risk of impurity generation and cross contamination. The factors influencing the flow are tabulated in Table 3. Understanding flow dynamics is critical in granulated powders, smart silo storage, and pharmaceutical processing, because it impacts segregation, uniformity, stability, and downstream manufacturing efficiency. These flow dynamics is used to describe the behaviour of powder and granules under various forces i.e. gravitational, shear and cohesive [31].

Table 3: Key Influencing Factors [28-31]

Factor	Impact on Flow
Particle size & distribution	Smaller, irregular particles leads to cohesiveness and poor flow
Shape	Spherical granules provided smooth flow; whereas interlocking result in poor flow
Surface properties	Rough or sticky surfaces increases friction leads to poor flow
Moisture content	High RH tend to caking, aggregation and flow obstruction
Bulk density & compressibility	High density may have better flow under gravity;
External forces	Vibration or aeration can enhance flow, prevent rat-holing

Hagen–Poiseuille analogue for powder flow : Following equation 1, is used for powder flow. Flow of granules increases with increase in sphericity, density and size. This ensures smooth flow in silos.

$$Q = k \cdot (\rho_b g)^{0.5} \cdot D_h^{2.5} \cdot (\tan\theta - \tan\theta_c)^{0.5} \quad \text{-------} \quad (1)$$

Where: Q = volumetric flow rate, k = flow coefficient (depends on particle properties), ρ_b = bulk density, g = gravitational acceleration, D_h = hopper diameter, θ = hopper angle and θ_c = critical angle of repose

5 CLOGGING OF ORAL SOLID DOSAGE IN SILOS

Clogging refers to the formation of stable structures, which either reduces flow or completely stops it. Thus, it becomes necessary to mitigate clogging. Clogging or blockages have critical impact on the flow of powder and granules in silos. It has major impact on stability of API, process control and manufacturing efficiency. Clogging

happens when material stop flowing due to interlocking of particles or due to cohesive nature.

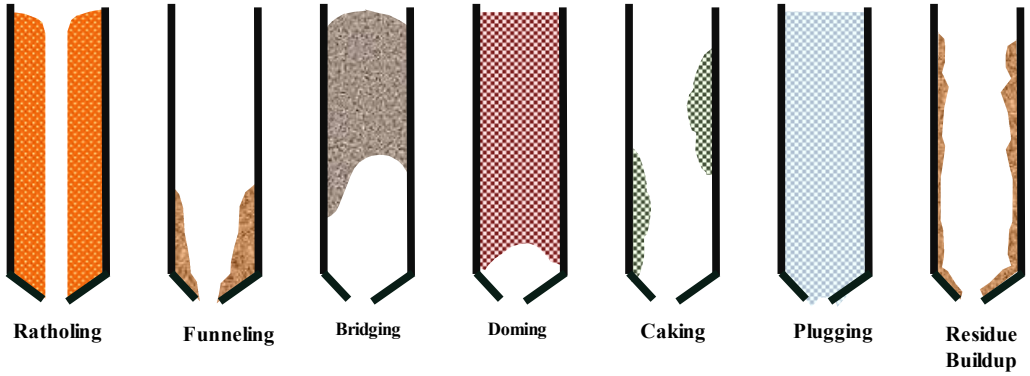

Figure 3: Different types of clogging (blockages)

Different types of blockages are mentioned in the Figure 3. When discharged through silos, these forms disordered arching, leading to clogging, thus creating operational challenges. This is mainly influenced by various parameters like size, shape of grains, silo geometry, etc. [31].

It is possible to obtain a set of parameters in which clogging can be avoided. Clogging of flow can also be mitigated by perfect design of silo geometry and does not require any energy input because flow occurs by self-weight. Discharge is governed by factors like particle characteristics (shape, friction, weight, and cohesiveness) and silo geometry, occurring due to the enhancement of stress transmission. Use of well-designed silo geometry can be the ideal method for enhancement of gravity flow. This is due to increase in gravitational stress which acts on arches to reduce bridge formation. Alternatively, it is possible to identify conditions where clogging-free flow is possible by addition of fines [32].

Table 4: Causes of Clogging [23,31,32]

Cause	Mechanism	Impact on Pharmaceutical Operations
Cohesive powders	Van der Waals, electrostatic, or moisture-induced adhesion	Sticking in hoppers, irregular flow
Fine particle size	High surface area; strong interparticle forces	Rat-holing or bridging, inconsistent dosing
Irregular shape	Needle-like or plate-shaped particles interlock	Mechanical jamming, arch formation
Moisture content	Hygroscopic powders absorb water to form bridges	Caking, reduced flowability, API degradation
Inappropriate hopper design	Shallow angles, narrow outlets	Funnel flow, stagnant zones, flow stoppage
Environmental conditions	Temperature and humidity fluctuations	Local condensation, agglomeration and clogging
Electrostatic charge	Dry powders develop charge particles stick to each other or walls	Flow interruption, adhesion to silo walls

Various mitigation strategies listed in Table 5 are used to reduce clogging. Granulation minimises the clogging. Binder coating reduces surface adhesion resulting in elimination of clogging [33].

Table 5: Mitigation Strategies for Clogging [27,30,33]

Strategy	Implementation	Pharmaceutical Advantage
Granulation optimization	Produce uniform, spherical granules	Reduced cohesion and bridging
Hopper design optimization	Steep angles, wide outlets, smooth walls	Promotes mass flow, prevents funnel flow
Environmental control	Control humidity & temperature via MPC	Avoid moisture-induced caking
Vibration or mechanical agitation	Periodic silo vibration	Breaks arches, prevents rat-holing
Aeration / fluidization	Inject air at silo bottom or sides	Reduces interparticle friction, enhances flow
Surface coatings	Low-friction coatings inside silo	Minimized adhesion of sticky powders

To avoid arching, following Critical Hopper Dimension Equation 2 is used.

$$D_c = k \cdot d \cdot \left(\frac{\sigma_c}{\rho g d}\right)^{0.5} \quad \text{-------} \quad (2)$$

Where, D_c = critical hopper diameter to avoid arching, d = mean particle diameter, σ_c = cohesive strength of powder, ρ = bulk density, g = gravity, k = empirical constant depending on hopper geometry

5 Segregation of Oral Solid Dosage in silos:

Segregation is defined as uneven distribution of components in a powder or granule mixture due to differences in size, density, shape, or flow properties. It leads to content uniformity problems in tablets, capsules, and other dosage forms [34] It may be occurred at any stage: granulation, hopper storage, silo discharge, and tablet compression. For uniform dosing, segregation is major concern. Segregation mechanism is classified as listed in Table 6.

Table 6: Mechanisms of Segregation [27,29,34]

Mechanism	Description	Relevance to Pharmaceutical Processing
Percolation / Sifting	Smaller particles move downward through voids between larger particles	Common during hopper discharge and silo storage, affects tablet uniformity
Trajectory / Rolling Segregation	Particles roll differently based on size and density on inclined surfaces	Granules flowing down chutes or silo hoppers
Fluidization Segregation	Lighter or finer particles are carried upward by airflow	During fluidized bed granulation or drying
Aggregation / Clumping	Cohesive fines stick to each other or to larger particles	Can reduce segregation but create flow variability
Density-based Segregation	Heavier particles settle, lighter particles rise	Critical in API-excipient mixtures, affects content uniformity
Electrostatic Segregation	Charged particles adhere to surfaces or repel others	In dry, low-humidity environments

Various factors such as particle size, shape, density, moisture content, vibrations, silo geometry, flow dynamics are influencing on the segregation. All these factors need to be carefully considered to control the segregation. Segregation in silos can result from different particle properties and can result in inefficiencies in operations resulting in inconsistent and variable product quality. This also affects the discharge rate of material. Segregation is the particle tendency to separate based on physical properties like shape, size, density and surface properties. The segregation issue is critical where uniform mixing is crucial. In pharmaceutical, it leads to inconsistent dosing resulting reduction in efficacy and leads to regulatory challenges. Granulation reduces segregation risk. Spherical granules result in uniform rolling, minimal percolation. Narrow particle size distribution leads to reduces size-based segregation. Binder coatings prevent fines from separating [35].

Simplified segregation equation 3 (percolation model) is stated below.

$$S = k \cdot (d_L - d_S) \cdot f(\rho_L, \rho_S) \cdot \sin\theta \quad \text{--------- (3)}$$

Where, S = segregation tendency, d_L, d_S = diameter of large and small particles, ρ_L, ρ_S = density of large and small particles, θ = slope of flow surface (hopper angle), k = empirical coefficient

Larger size or density differences leads to higher segregation risk whereas steeper hopper angles exacerbate segregation [36]. Various mitigation strategies are listed in Table 7.

Table 7: Mitigation Strategies for segregation [24,36]

Strategy	Implementation	Pharmaceutical Benefit
Granule uniformity	Control size, shape, density during granulation	Reduces percolation & density segregation
Binder and coating	Adhesion of fines to larger granules	Prevents fines from separating
Hopper design	Steep walls, mass flow design	Minimizes funnel flow & stagnant zones
Controlled feeding & discharge	Use of feeder screws or vibratory feeders	Smooth flow reduces trajectory segregation
Aeration & vibration	Reduce cohesive arches and stagnant regions	Enhances uniform mass flow
Blend optimization	Pre-blending of API and excipients before granulation	Uniform mixture reduces segregation risk

Selection of appropriate drug formulations is based on the assessment of various factors. This includes releasing profile, properties of active pharmaceutical ingredients, and patient need. Continuous manufacturing are adopted to integrate unit batch operations into continuous processes. This results in efficient and cost effective OSD manufacturing [37]. To meet the required quality standards, testing is an essential criterion. Various critical process parameters, its mechanism and impact are tabulated in Table 8.

Table 8: Critical Process Parameters [25, 35,37]

Parameters	Mechanism	Impact
Flowability	Cohesive arching, ratholing, wall friction	Weight variation, erratic hopper discharge
Uniformity	Percolation, fluidization segregation	Content uniformity failures, dose dumping
Impurities	Defective crystallization, side-reactions	Altered dissolution, chemical degradation
Contamination	Equipment wear, poor sanitation	Extreme safety risks, toxicological reactions

The potential challenges related to handling of powders and granules are listed in Table 9, providing insight into the factors affecting drug delivery systems [38].

Table 9 Potential challenges in Pharmaceutical Powder Processing [27,37,38]

Challenge	Mechanism	Impact	Mitigation
Moisture / Caking	Hygroscopic absorption	Poor flow, API degradation	Relative Humidity control, coatings, desiccants
Electrostatics	Triboelectric charging	Wall adhesion, uneven flow	Grounding, ionization, humidity
Thermal / Chemical Instability	Heat, exothermic reactions	Degradation, polymorphism	Temp control, digital twin monitoring
Dust / Safety	Fine powders	Explosion, inhalation risk	Granulation, enclosed handling, filtration
Mechanical Attrition	Vibration, handling	Fines, segregation	Optimize granule hardness, reduce stress
Contamination	Cross-contact	Regulatory failure, potency issues	Dedicated silos, Cleaning in place (CIP)/System in place (SIP), liners

6. SIMULATION IN GRANULES AND SILOS

Discrete element method is used to predict flowrate. It also describes the stagnant zone and indicates the stress point in the silo. Digital twin silos integrate simulation and real time data. This benefits to enhance flow, reduction in clogging and control of segregation. Model predictive control is used to adjust the environmental parameters based on predicted flow. DEM predicts the critical outlet opening diameter for clog-free flow. Poor flow behaviour results funnel flow and stagnant zones leading to segregation. Granulation improves flow and packing density, directly reducing segregation [39].

7. TECHNOLOGICAL ADVANCEMENT

To control storage parameters and environment inside the silo, automation employment is needed of time. This automation is also important from safety aspects. Automation is basically classified as: Basic, integration, process and Artificial intelligence (AI). Research has developed smart devices for specific storage of grains. Integration of advanced technologies like smart sensors along with internet of things (IoT) are useful to enhance storage. These sensors are used in detecting and controlling the above environmental parameters. Though IoT has great scope, it is having limitations such as high capital cost, data integrity and security, and lack of knowledge to the farmers [40].

Artificial intelligence is exhibited by machine intelligence. It is automated system which has ability to do tasks that need human intelligence. This has proven to be the fastest emerging technology. AI consists of smart sensors to process real time data with high level of accuracy, precise sensing and prompt transmitting of data with immediate outcome. This artificial intelligence along with various smart sensors leads to further advanced automation technology, widely known as Internet of Things (IoT). Hence IoT based AI, and digital technologies are having potential to provide innovative modelling of silos for grains [41].

Various analytical and computational methods are used to envisage, analyse and optimize flow behaviour, silo design and to prevent operational problems of clogging, plugging for ensuring efficient flow [42]. Each methods offer distinct advantages to optimize the flow of granular materials through silos. For spherical particles, continuum and empirical models serve the purpose. However, for non-spherical particles, methods like Discrete Element Modelling (DEM), Visco-Elastic Models, and Lattice Boltzmann Methods (LBM) provide more detailed and accurate complex particle interactions, shapes and behaviours. These methods also predict and mitigate issues of clogging, bridging, and uneven discharge, resulting in optimized silo design [43].

Future Perspective:

Future pharmaceuticals and formulation are evolving towards advanced continuous manufacturing. This also assisted with high level of automation and supported with advanced process technologies, predictive tools for modelling and artificial intelligence. To enhance powder flow dynamics, mitigation of clogging behaviour, control of segregation mechanism needs to be properly understood to facilitate robust quality by design (QbD) next generation drug delivery systems. To enhance manufacturing efficiency, product quality, regulatory compliances and therapeutic reliability, advanced particle engineering, simulation and integration of digital processes needs to be implemented across the pharmaceutical product lifecycle. Advanced containment technology and closed system manufacturing is going to be crucial for highly potent drugs to minimise occupational exposure of the drug and to eliminate cross contamination risk. Regulatory agencies may encourage advanced technologies for real time release testing. Development of multi-functional, environment free excipients benefit to drug delivery performance by enhancing flowability, moisture resistivity, anti-static behaviour. Development of sustainable, energy efficient, solvent free processing methods is expected to become major focus in pharmaceutical manufacturing.

RESEARCH GAP

Due to Complexity of API materials, Multiphysics interactions, data limitations and regulatory constraints, significant scientific and engineering challenges are encountered. However, these challenges also represent major research opportunities, especially in hybrid modelling, digital twins, explainable AI, Real-time predictive systems. No dedicated, validated modelling frameworks is available for pharmaceutical APIs, which

exhibit complex degradation kinetics and hygroscopic and polymorphic behaviour. Current models often treat processes independently, i.e. heat transfer, moisture diffusion and chemical degradation. It is having lack of fully coupled Multiphysics models that simultaneously simulate temperature humidity oxygen exposure and API degradation kinetics. For accurate, real-time prediction of API stability, integration of mechanistic and AI models are not sufficient. Real-time predictive frameworks is lacking for forecasting degradation and estimating shelf-life. Digital Twin has limited application in pharmaceutical storage and having lack of Real-time synchronization. It is needed to have or Explainable AI models that meet GMP and regulatory compliances. Most models are lab-scale and theoretical lacking industrial-scale validation and benchmarking.

CONCLUSION

Impurities and contamination are major concerns in pharmaceutical and formulation. Effect of flow dynamics, clogging behaviour and segregation mechanism on these is discussed in depth.

The influence of excipient properties on API flowability, electrostatic charging, and impurity distribution requires further mechanistic investigation, particularly in low-dose formulations. Research on environmentally sustainable pharmaceutical powder processing technologies, including reduced material loss and energy-efficient handling systems, is still limited. This review article will guide researchers and industrialists to simulate the interaction from raw material to finished dosage form ensuring drug safety and efficacy from manufacturing active pharmaceutical ingredients to clinical drug delivery. Continuous manufacturing ensures the fidelity in the quality of product, which further assures the therapeutic performance from active pharmaceutical ingredient to final clinical drug delivery.

NOMENCLATURE

API – Active Pharmaceutical Ingredient
OSD – Oral solid dosage
QbD – Quality by design
AI – Artificial Intelligence
IoT – Internet of Things
GMP – Good manufacturing practices
CIP – Cleaning in place
SIP – System in place
DDS – Drug Delivery System

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