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Review Article

Physicochemical Comparison of Pharmaceuticial Powders and Granules

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ABSTRACT

A The present study involves a comparative analysis of powders and granules formulated using a BCS Class I drug, which is characterized by high solubility and high permeability. The objective of the study is to evaluate and compare the physicochemical properties, flow behavior, and drug release profiles of the two formulations. Preformulation parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio were assessed to determine flow characteristics. In addition, in vitro dissolution studies were conducted to analyze drug release patterns. The results indicated that granules exhibited improved flow properties and better compressibility compared to powders, contributing to enhanced uniformity and processability in tablet manufacturing. Drug release from both forms was comparable due to the inherent solubility of the BCS Class I drug. The study concludes that granulation is a preferred technique for improving handling and processing characteristics without compromising drug release efficiency.

INTRODUCTION

Oral administration is the most common method of treating both local and systemic gastrointestinal conditions. Despite of the apparent benefits, oral administration is still difficult because of the harsh gastrointestinal tract (GIT) milieu and several physiological barriers, such as gastrointestinal anatomical factors, biochemical factors, and physiological factors. Absorption of food and absorption of drugs depend on the many components of the gastrointestinal tract (GIT), which include the mouth cavity, oesophagus, stomach, small intestine, and colon. Various anatomical features, including the gastric mucin–bicarbonate barrier, enteral enzymes, and the oral cavity's limited surface area, may also impede the absorption of drugs. Much work has been done to address these problems, which are mostly based on a better understanding of the GIT's healthy and diseased physiological characteristics [1]. The oral pathway has drawn the most attention among the different drug delivery methods because of its

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distinct benefits, which include easy administration, sustained and controlled delivery, the possibility of solid formulations, patient compliance, and, in the case of vaccines, an enhanced immune response. A high surface area (>300 m2) that is bordered with a viscous mucosal layer also facilitates drugs adhesion and absorption [2]. Additionally, the shear stresses brought on by the flow of stomach secretions are prevented from harming medication molecules that are trapped in mucus.Due to the large number of enterocytes in various intestinal regions, particularly the microfold cells (M cells) that cover the Peyer's patches, the lymphoid section of the small intestine, the human intestinal epithelium is highly absorbent[3]

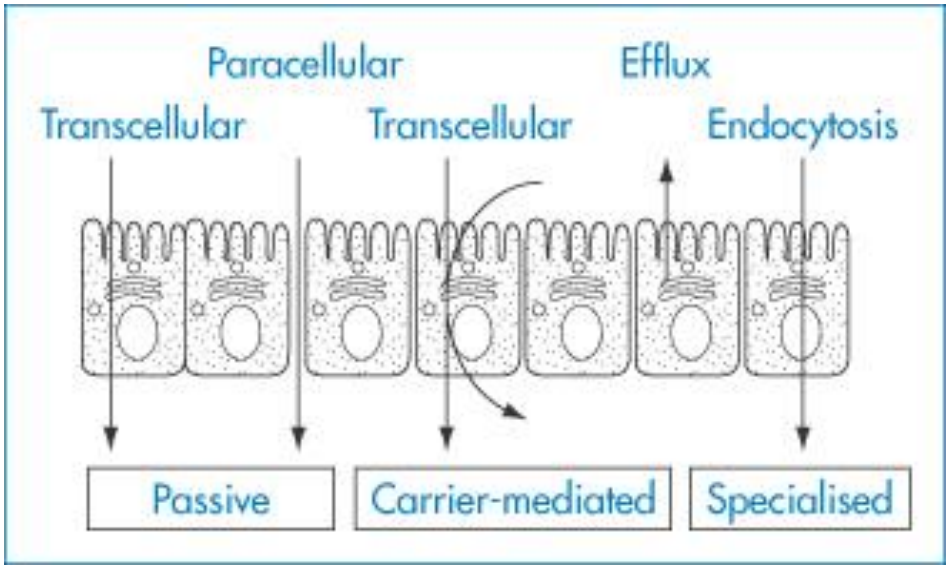

Fig 1 Pathways of Drug absorption

However, the mechanism of drug absorption is more complicated than that of other routes. For oral medications to be absorbed in GIT, they must dissolve in gastric fluid. There are four different methods that drugs taken orally can be absorbed: assisted transport, transcellular, paracellular, and carrier-mediated transcellular. The transcellular route is the primary mechanism among these pathways [4]. Drugs aqueous solubility and intestinal epithelial membrane permeability are important factors that determine GI absorption; the Biopharmaceutical Classification System (BCS) uses these factors to divide medications into four groups. The largest dose strength that can dissolve in a glass of water (250 ml; volume) or less in aqueous media (pH 2–7.5) is the basis for the BCS's solubility requirements. The diffusion of a drug across the apical membrane of enterocytes into the cytosol is known as permeability, and it is dependent on the drug's polarity, charge, and lipophilicity. A medication is considered extremely permeable if it absorbs at least 90% of the dose that was given.BCS Class I drugs are suitable for oral administration due to their high permeability and solubility. On the other hand, because of their low permeability (BCS Class III), low solubility (BCS Class II), or both (BCS Class IV), other BCS classes are difficult candidates for oral delivery. Increasing the dissolving rate of BCS Class II medications can enhance their oral absorption capacity [5].

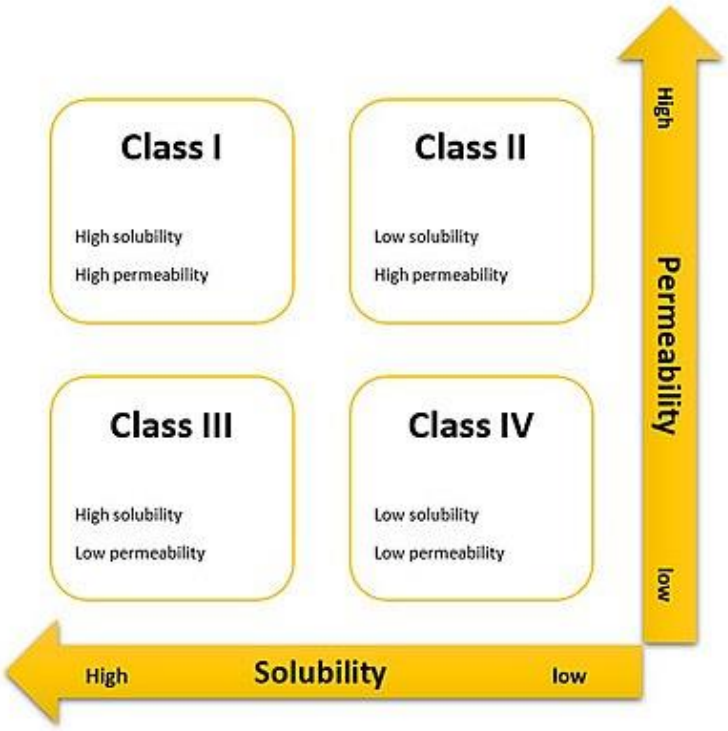

Fig 2 BCS Classification

BCS is based on the principle that two medicinal items that produce the same concentration profile along the gastrointestinal (GI) tract will also produce the same plasma profile when taken orally. Fick's first can be used to summarize this idea in the following equation.J = Pw Cw…….(1) where Cw is the concentration profile at the gut wall, Pw is the permeability of the gut wall to the drug, and J is the flux across the gut wall. Unless significant formulation changes are made, it is assumed that highly permeable, highly soluble drugs contained in rapidly dissolving drug products will be bioequivalent. Additionally, dissolution data can be used as a stand-in for pharmacokinetic data to demonstrate bioequivalence[6].

BCS Classes:

Class I drugs : They exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. Bioavailability and dissolution is very rapid. So bioavailability and bioequivalency studies are necessary for such product. IVIVC cannot be expected. These compounds are highly suitable for design the SR and CR formulations. Examples include Ketoprofen, Naproxen, Carbamazepine, Propanolol, Metoprolol, Diltiazem, Verapamil etc [7,8].

Class II drugs: They have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. Thes drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. In vitro-In vivo correlation (IVIVC) is usually expected for class II drugs. Examples include Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine, Felodipine, Nicardipine, Nisoldipine etc [8].

Class III drugs:The rate-limiting phase in medication absorption is permeability. The rate and degree of drug absorption varies greatly for these medications. The fluctuation can be attributed to changes in physiology and membrane permeability rather than dosage form considerations because of the quick breakdown. These medications present challenges for the development of controlled release. These medications need improvement in permeability and shown limited bioavailability. Examples are Acyclovir, alendronate, captopril, enalaprilat, neomycin B etc [7]. Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability and gastric emptying form the rate limiting steps for the drug absorption. These are unsuitable for controlled release. Examples include Chlothaizude, Furosemide, Tobramycine, Cefuroxime etc [9].

Exception for BCS

BCS-based biowaivers are not applicable for the following:

1. **Narrow Therapeutic Range Drugs**: Products with specific drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, as well as those whose labeling specifies a narrow therapeutic range designation, are classified as narrow therapeutic range drugs under this advice. Theophylline, warfarin, digoxin, and lithium phenytoin are a few examples. Sponsors should assess if a drug should be classified as having a narrow therapeutic range by contacting the relevant review division, as not all medications that are subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range medications [6].
2. **Products Designed to be absorbed in the Oral Cavity:** A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g. sublingual or buccal tablets) [6].

BCS-1 drug : Lacosamide

The antiepileptic drug (AED) lacosamide, which comes in a number of forms, was first approved in 2008 for use as an adjuvant treatment for adults with partial onset seizures (POS) [10]. People of all ages can suffer from epilepsy, a chronic, noncommunicable brain disorder. The World Health Organization estimates that 50 million individuals worldwide, of all ages, suffer from epilepsy, making it one of the most prevalent neurological conditions. Individuals, families, and society as a whole may suffer greatly from epilepsy alone [11]. To exacerbate the situation, more than 50% of people with epilepsy also have psychological comorbidities. Psychosis of epilepsy (POE) is a common term used in the medical literature to describe the psychotic condition that affects individuals with epilepsy. This phrase refers to a collection of mental illnesses that may be strongly associated to seizures and have distinct phenomenologies and pathophysiologies. Specifically, POE refers to psychotic symptoms, which include delusions, hallucinations, severely disordered or catatonic behavior, and negative symptoms that worsen with preserved consciousness [Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)/DSM-V]. It excludes other mental illnesses including obsessive-compulsive disorder, bipolar disorder, depression, and so on [12]. People suffering from epilepsy frequently experience focal or widespread unprovoked (spontaneous) seizures. Although several antiseizure medications (ASDs) may have been

used separately or in different combinations, around one-third of individuals with epilepsy are unable to completely control their seizures; this is known as drug resistance. Theoretically, there are at least four distinct clinical forms of medication resistance: 1) de novo ASD resistance, in which the patient never experiences a useful period of seizure-free living from the moment the epilepsy begins; 2) delayed resistance, in which the patient initially stops having seizures but later experiences recurrent seizures that are uncontrollable; and 3) a waxing-and-waning (fluctuating) pattern, in which the epilepsy alternates between being controlled and uncontrolled; 4) Initially resistant to medications, eventually responds to therapy[13]. According to long-term outcome studies conducted on recently treated epileptic patients, the likelihood of success with additional medication manipulation decreases gradually when two well-tolerated ASD regimens that are suitably selected for the seizure type or types fail. The idea that drug resistance is established de novo in many individuals is thus supported by the fact that drug-resistant (medically refractory) epilepsy is frequently detected early in the course of treatment [14]. Although the number of stroke survivors who live with morbidities has significantly grown, stroke mortality has dramatically decreased as a result of advancements in stroke therapy. Poststroke seizures and epilepsy (PSSE) has been recognized as a significant clinical problem with both medical and psychosocial components. Epilepsy and seizures are frequent morbidities among stroke patients. The most frequent cause of epilepsy in older persons (those 65 and older) is stroke [15]. Given the high rate of seizure recurrence following the initial poststroke unprovoked seizure, the European Stroke Organization's recommendations for managing PSSE advocated the use of supplementary antiseizure drugs (ASMs) as a preventative measure. Using the Taiwan National Health Insurance Research Database (NHIRD), a sizable, countrywide population-based study evaluated the effectiveness of several ASMs in managing poststroke epilepsy. In order to treat poststroke seizures, phenytoin was prescribed to the majority of patients (69%) followed by valproate (20%), carbamazepine (4%), and novel ASMs (oxcarbazepine, vigabatrin, tiagabine, topiramate, gabapentin, levetiracetam, and pregabalin; 7%) [16]. In an effort to address the causes and mechanisms of epilepsy rather than its symptoms, new-generation ASMs are anticipated to provide seizure control with fewer side effects and drug-drug interactions. Harris Corporation made the first discovery and development of lacosamide, formerly known as harkoseride. It was then licensed to Schwarz Pharma AG, which UCB S.A. (Brussels, Belgium) purchased a few years later, to treat neuropathic pain and epilepsy. This third-generation ASM was first authorized in 2008 as a supplement for seizures with partial onset, whether or not secondary generalization is present. The European Medicines Agency (EMA) and Food and Drug Administration (FDA) later authorized it as a monotherapy for partial onset seizures in 2014 and 2016 [17]. Lacosamide is an effective and safe supplementary treatment for uncontrolled primary generalized tonic-clonic seizures in individuals with idiopathic generalized epilepsy, according to a recent study by Vossler et al. In fact, the FDA, EMA, and Pharmaceutical and Medical Devices Agency all approved it for this use. It comes in intravenous (IV) solution, syrup, and tablet form. As an adjuvant treatment, the dosage should be titrated up to 400 mg, and as a monotherapy, it should be 600 mg per day [18]. Lacosamide selectively encourages delayed inactivation of sodium channels, which is different from traditional sodium channel blockers. Without impairing physiological function, this mechanism of action stabilizes hyperexcitable neuronal membranes, suppresses neuronal firing, and

lowers long-term channel availability [19]. Lacosamide has an excellent and well-studied pharmacokinetic profile that includes a minimal risk of drug-drug interactions, a rapid rate of absorption, and little to no interaction with cytochrome P-450 izoenzymes [20]. The clinical development of lacosamide included three double-blind, randomized, placebo-controlled investigations with over 1,300 participants.When compared to a placebo, each of these trials demonstrated the safety and efficacy of lacosamide as an extra treatment for people with POS. The clinical use of lacosamide may increase based on the results of studies looking at its use as a monotherapy for POS in adults, as a treatment for epilepsy in children, and as an adjuvant therapy for uncontrolled primary generalized tonic-clonic seizures in individuals with idiopathic generalized epilepsy [21]. Unlike traditional sodium channel blockers (SCBs), which work by inactivating voltage-gated sodium channels quickly, lacosamide works by inactivating them slowly. The most recent SCB, eslicarbazepine, improves both the slow and fast inactivation mechanisms. The topic is still up for debate because a number of research that looked into the relationship between lacosamide and SCBs or non-sodium channel blockers (NSCBs) found either no difference or worse tolerability and effectiveness [22]. In actual practice, lacosamide is evidently effective when used in typical patients with focal-onset epilepsy.On the other hand, although approximately one-fourth of epileptic patients have an intellectual impairment, there is, at best, little data on the usage of lacosamide in populations of patients with drug-refractory epilepsy, who are frequently impacted by neurological and intellectual disabilities[23]. The high rate of medication refractoriness, which can reach 68%, and the difficulty of assessing the tolerability and effectiveness of AEDs—since people are sometimes unable to discuss the effects of AEDs—are major issues in the management of patients with epilepsy and intellectual disabilities [24]. Lacosamide IR tablets (VimpatTM, UCB Pharma, Inc., Smyrna, GA) are authorized for use as a primary generalized tonic-clonic seizure adjunctive treatment as well as a monotherapy treatment for partial onset seizures in a wide range of age groups in numerous countries. Lacosamide IR tablets have a time to Cmax of roughly 1-4 hours, an elimination half-life of roughly 13 hours, and a dose-proportional pharmacokinetic (PK) profile spanning 100-800 mg. When taking lacosamide IR tablets as monotherapy, adults should take 150–200 mg twice daily (BID) for a daily total of 300–400 mg. As a once-daily (QD) formulation, Lacosamide XR capsules (Motpoly XR™, Aucta Pharmaceuticals, Inc., Piscataway, NJ) have been approved by the US Food and Drug Administration (FDA) to treat partial onset seizures in adult and pediatric patients [25]. Recent technological advancements have led researchers to create FDTs that are more convenient and patient-compliant. It might be difficult for many older individuals to swallow powders, tablets, or capsules. These tablets are supposed to dissolve or disintegrate in the oral cavity without the need for drinking water in order to solve this issue. Disintegrates are added to fast-dissolving tablets to improve dissolve by accelerating tablet disintegration. Since disintegration is crucial to a tablet's eventual release of the active therapeutic ingredient from the tablet's structure into the body, the kind, concentration, and effectiveness of disintegrants greatly influence the disintegrating qualities [26]. Nowadays, the majority of active pharmaceutical ingredients (APIs) are fine powders with a size distribution of 100 μm or less. Furthermore, particles smaller than 30 μm are the ongoing concern and very challenging to control. Strong inter-particle interactions including van der Waals, capillary, and electrostatic forces are mostly to blame for this. The van der Waals

interaction is the primary aspect influencing powder cohesiveness for fine, dry particles. Small amounts of flow additives known as glidants are added, along with techniques like aeration and vibration, to make handling these tiny powders easier [27]. Powder is a dry mixture of finely divided drug and/or chemicals that can be applied topically (topical or dusting powder) or taken inside (oral powders). In BP (British Pharmacopeia), powders are classed as solids based on the size of their constituent particles, which range from 1.25 µg to 1.7 mm in diameter. Another way to categorize powders is by the manner in which they are dispensed [28]. Pharmaceutical powders are defined as heterogeneous systems that has a range of particle sizes from a few micrometers to roughly a millimeter, with varying physical and/or chemical composition. On average, about 80% of the manufacturing facilities in the pharmaceutical business is based on tablet powders. For these reasons, understanding and controlling the physical behavior of powders is essential when creating and processing solid dosage forms. In a number of unit activities, including blending, compression, filling, transportation, and scale-up operations, the flow behavior of the powder is crucial [29]. The majority of processes in the pharmaceutical industry, including sieving, pouring, micronizing, mixing, pneumatic conveying, grinding, drying, and compaction, are related to the flowability of the powder. Drug dosage and, thus, pharmacological impact are entirely dependent on factors such as the powder's ability to be fed into a press die prior to compression. To generate final products with an acceptable homogeneity content, weight fluctuation, and physical consistence, the ideal powder flow must be accomplished during the compression of tablets and the filling of capsules [30]. Particle size, size distribution, shape, surface energy, surface texture, chemical makeup, moisture content, vessel geometry, and other elements all influence the manner in which powder flows. Many techniques, mostly based on empirical knowledge, have been developed to measure powder flowability in response to this complexity. The measurable outcomes of these techniques are not always reliable in practice and might be challenging to understand [31]. Granulation is a particle enlargement technique used in pharmaceutical and other industries. High-shear granulation produces dense granules quickly. An active ingredient is often mixed with fillers and additional excipients in pharmaceutical formulations. The filler's characteristics mostly determine the granules' characteristics. Certain fillers, such microcrystalline cellulose, or MCC, readily form smooth, spherical granules, whereas others result in rough or uneven granules [32]. Considering the variety of granular materials and powders utilized in many different sectors and their wide range of applications, a thorough understanding of their macro- and micro-mechanical behavior is necessary.Granular material is made up of different particles that interact with one another and lose energy. In general, whether a material is granular is determined by its particle size. Granular materials must have a minimum particle size of 1 µm; smaller materials may be subjected to oscillations caused by thermal motion [33]. Finding the ideal formulation during the drug development stage requires careful assessment of the flow characteristics. Parameters like the Hausner ratio, compressibility index, also known as Carr's index, and angle of repose are typically used to determine the powder flow characteristics. These techniques are frequently utilized in industrial applications and scale-up operations, are easy to use, and are advised by pharmacopeias to assess the flowability of powders [34]. The steepest slope of the unconfined material, measured from the horizontal plane on which the material can be heaped without

collapsing, is one of the most widely used definitions of the angle of repose[35].

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

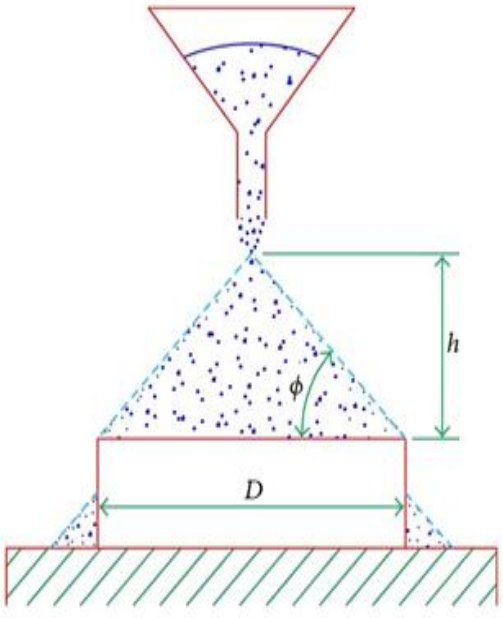

Fig 3 Fixed Funnel Method [36]

The Hausner ratio or the tapped-to-bulk density ratio is commonly used to describe the angle of repose for powders, which are small granular materials that are prone to cohesion and suspension in a gas. Powders will flow at angles larger than the angle of repose. Using the Carr classification of flowability, the angle of repose can also reveal how cohesive the granular material is[37].

Description	Angle
Very free-flowing	<30°
Free flowing	30–38°
Fair to passable flow	38–45°
Cohesive	45–55°
Very cohesive (non-flowing)	>55°

When describing and processing powder systems, bulk density is a crucial physical characteristic. It is calculated by dividing the mass by the total volume occupied while accounting for the spaces that exist between particles in a powder bed. The two most prevalent bulk densities are tapped bulk density (ρtap) and loose poured bulk density (ρLB). The density of a powder that is poured into a container and given time to settle is known as the loose poured bulk density; it is a measurement of randomly loose packing. Tapped density, a measurement of random dense packing, is the density that results from densifying a loosely packed powder bed using an external force to

create higher particle packing [38]. Because the interparticulate interactions that affect a powder's bulking qualities also affect its flow, a comparison of the bulk and tapped densities might provide insight into how important these interactions are in a particular powder. Such a comparison, such as the Compressibility Index or the Hausner Ratio as explained below, is frequently employed as an indicator of the powder's flowability [39]. As previously mentioned, the Compressibility Index and Hausner Ratio are indicators of a powder's propensity to compress. They thus serve as indicators of the powder's settling capacity and enable a determination of the relative significance of interparticulate interactions.Such interactions are less important in a free-flowing powder, since the values of the bulk and tapped densities will be closer. A larger gap between the bulk and tapped densities will be seen in materials with poor flow because there are often more interparticle interactions. The Hausner Ratio and the Compressibility Index both show these variations [40].

Compressibility index= $100(V_0-V_f)/100$

Hausner ratio = V_0/V_f

V_0 = unsettled apparent volume; V_f = Final tapping volume

Bulk density, also called apparent density, is a material property defined as the mass of the many particles of the material divided by the bulk volume. Bulk volume is defined as the total volume the particles occupy, including particle's own volume, inter-particle void volume, and the particles' internal pore volume [41]. Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The tapped density of a powder represents its random dense packing. Tapped density can be calculated using the formula; Tapped Density (g/mL) =M/V_f

where M=mass in grams, and V_f=the tapped volume in millilitres [42].

Key Differences Between Powders and Granules

Powders, which are finely divided solids, provide flexibility for compounding and can be used as a precursor for other dosage forms like capsules and suspensions. However, powders are more prone to segregation issues and may present challenges in ensuring uniform distribution of the active pharmaceutical ingredient (API) across the batch.

Granules, on the other hand, offer improved flow properties and compressibility, making them a preferred intermediate for tablet production. Their larger particle size compared to powders reduces dust generation and enhances the safety and ease of handling during the manufacturing process.

ASPECT	POWDERS	GRANULES
FORM	Fine particles, loose powder	Agglomerated small particles
FLOWABILITY	Poor	Good
COMPRESSIBILITY	Very low	Improved due to particle size
SURFACE AREA	Largest (highest surface area per unit mass)	Less than powders, due to particle agglomeration
DISSOLUTION RATE	Fastest	Moderate
MANUFACTURING COMPLEXITY	Simple	Moderate
PATIENT CONVENIENCE	Low	Moderate
STABILITY	Variable (prone to moisture absorption)	More stable than powders
USAGE	Flexible (used in bulk formulations, suspensions)	Often used in controlled-release formulations

CONCLUSION: The comparative study of powders and granules containing a BCS Class I drug demonstrated that granules possess superior flow properties, compressibility, and handling characteristics compared to powders. While both formulations showed effective drug release due to the high solubility and permeability of the BCS Class I drug, granules offered better suitability for large-scale manufacturing and consistent dosage form production.The study concludes that granulation is a preferred technique for improving handling and processing characteristics without compromising drug release efficiency. Therefore, granulation can be considered a more efficient and reliable formulation approach for BCS Class I drugs in terms of both processing and product performance.

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