

Fundamental Mechanisms of Powder Caking: Linking Interparticle Adhesion to Bulk Behavior Using Lactose as a Model System

1. Background and State of the Art

Powder caking arises from attractive interparticle forces that sustain contact long enough for more permanent bonds resulting in solid bridges between the particle. Extensive theoretical frameworks exist for van der Waals, capillary, and electrostatic forces, as well as for elastic and plastic contact mechanics. However, as highlighted in the *Powder Caking A review for IFPRI (SAR 16-11)* underpinning this proposal, these frameworks largely address equilibrium or idealized conditions and fail to capture irreversible, non-equilibrium contact evolution that dominates real caking scenarios.

Solid bridge formation through sintering, viscous flow, dissolution-recrystallization, and solvent evaporation has been identified as the central mechanism driving caking. Yet, research on sintering and diffusion mechanisms originates primarily from powder metallurgy and ceramics, operating at temperatures and stresses far larger than those relevant for storage and handling of powders. The applicability of these concepts to powder caking under moderate temperature and humidity remains largely unexplored.

Amorphous powders have received significant attention due to their pronounced caking tendency above the glass transition temperature T_g , especially in the presence of moisture. While promising kinetic models exist, the behavior of multi-component systems, particularly mixtures of amorphous and crystalline particles remains poorly understood so far. Experimental evidence suggests that solid bridges in such systems are often metastable, evolving over timescales of weeks or months, but systematic studies are lacking.

In industrial practice, powder stickiness and caking propensity are commonly assessed using bulk methods such as dynamic vapor sorption (DVS) with relative humidity ramping, differential scanning calorimetry (DSC) for glass transition temperature (T_g), and dynamic tests including rotating drums or fluidized beds. These techniques typically yield a characteristic “stickiness onset” or T_g -like value that is interpreted as a bulk material property. However, these measurements reflect equilibrium or quasi-equilibrium behavior of the entire powder bed and inherently average over heterogeneous local environments and contact conditions.

Importantly, such bulk techniques cannot resolve the localized physicochemical processes occurring at individual particle-particle contacts, where curvature-induced vapor concentration, capillary condensation, and stress-assisted phase transitions may lead to premature softening, viscous flow, or amorphization. As a result, the onset of stickiness and irreversible contact formation may occur at relative humidities or temperatures significantly lower than those inferred from bulk T_g or DVS measurements. This discrepancy highlights a critical knowledge gap between industrially applied stickiness tests and the microscale mechanisms that ultimately govern powder caking.

The review explicitly identifies the absence of direct, time-resolved measurements of interparticle adhesion and solid bridge evolution as a major obstacle. Techniques such as AFM colloid probe measurements and NMR are recognized as promising but remain underutilized and rarely combined with rigorous mechanical testing.

This project directly addresses these gaps by integrating single-contact measurements, bulk rheology, and molecular-scale characterization within a unified experimental framework.

2. Objectives and Research Questions

The overall objective of this project is to establish a fundamental, quantitative understanding of powder caking by linking microscale interparticle interactions, solid bridge formation, and macroscopic bulk behavior, using lactose powders as a well-defined and industrially relevant model system under controlled temperature and humidity conditions. Lactose powders are selected as a model system due to their well-defined crystalline and amorphous forms, sensitivity to humidity and temperature, and widespread use as a reference material in caking research and industrial formulations. This objective is addressed through the following five research questions:

1. How do temperature and humidity control interparticle adhesion, capillary effects, and irreversible contact formation between lactose particles at the single-contact level?
2. Which mechanisms dominate solid bridge formation in lactose powders, and how do these bridges evolve and age over time under constant sub-deliquescent environmental conditions?
3. How can microscale adhesion forces and solid bridge strengths measured between lactose particles be quantitatively correlated with macroscopic caking and flow behavior?
4. How do stickiness and glass transition onsets determined by bulk methods (DVS, DSC, rotating drum or fluidized bed tests) compare to the onset of adhesion and irreversible contact formation observed at the single-particle level using AFM under identical thermo-hygrometric conditions?
5. How does the coexistence of amorphous and crystalline lactose phases influence moisture uptake, solid bridge formation, and caking kinetics in mixed systems?
6. How do molecular mobility and water distribution in lactose powders, as measured by NMR, govern the onset and progression of caking?

3. Research Group Activities

Aggregation, agglomeration, and caking phenomena are governed by chemical and physical adhesion forces acting between individual particles. A central theme of my research group's activities is the fundamental investigation of these adhesion forces and their role in determining the structure, stability, and flow behavior of particulate systems.

In previous and ongoing work, our group has focused on the formation of agglomerates, where particle-particle adhesion directly controls agglomerate size, morphology, and resulting material properties. To achieve a fundamental understanding at the smallest relevant length scale, we have developed an AFM-based methodology that enables the direct measurement of adhesion forces between individual nanoparticles. These experimental results have been backed up with molecular dynamics simulations, leading to the development of a physically grounded adhesion model for nanoparticles in gaseous environments.

Building on this foundation, the research group is currently engaged in several projects aimed at extending the fundamental understanding of interparticle adhesion across relevant particle size ranges and environmental conditions, including variations in humidity, temperature, and liquid environments. A key objective of these efforts is to establish quantitative, theory-based models of adhesion that can be directly linked to the flow and mechanical behavior of particulate systems, with the long-term goal of replacing purely empirical flow models with predictive models grounded in interparticle physics.

Therefore, our laboratory is equipped with advanced atomic force microscopy that allow direct adhesion measurements under controlled humidity, temperature, and electrochemical conditions. Since interparticle adhesion is intrinsically linked to surface chemistry and physicochemical properties, necessary characterization techniques are available, including BET surface area analysis, thermogravimetric analysis (TGA), FTIR spectroscopy, and wetting characterization using Washburn methods. Particle size and morphology are characterized using dynamic light scattering (DLS), scanning and transmission electron microscopy (SEM, TEM), and optical microscopy.

The proposed project on the fundamental mechanisms of powder caking in lactose-based systems directly leverages therefore our expertise. It represents a natural extension of the group’s ongoing efforts, shifting the focus from nanoparticle adhesion and agglomeration toward industrial particle adhesion, solid bridge formation, and bulk caking behavior in cohesive powders.

4. Methodology and Work Plan

The project is structured into five interlinked work packages (WPs):

WP 1: Preparation and Physicochemical Characterization of Lactose Model Powders	
Aim	Establish well-defined lactose-based model systems with controlled phase composition and surface properties.
Task	Preparation of crystalline lactose (α - and β -lactose where applicable), amorphous lactose, and mixed amorphous-crystalline lactose powders with controlled particle size distributions.
	Characterization of surface area, porosity, and morphology using BET and microscopy.
	Measurement of moisture uptake and thermal behavior using TGA.
	Optical and electron microscopy to assess morphology and surface features.
	Determination of bulk moisture sorption isotherms and apparent stickiness or T_g -like transitions using dynamic vapor sorption (DVS) with controlled RH ramping.
	Establishment of reference states for subsequent single-contact and bulk experiments.
	Reference glass transition measurements using DSC where applicable, to establish bulk thermal benchmarks.
Outcome	A library of reproducible lactose powders enabling systematic investigation of caking mechanisms as a function of phase composition and environmental conditions.

WP 2: Single-Contact Adhesion and Irreversible Contact Formation in Lactose Powders	
Aim	To quantify interparticle adhesion forces and irreversible contact formation between lactose particles under controlled temperature and humidity.
Task	Colloid probe AFM measurements using lactose particles in particle-particle and particle-substrate configurations.
	Systematic variation of relative humidity and temperature to probe capillary condensation, surface softening, and viscous flow effects.
	Measurement of pull-off forces, adhesion hysteresis, contact area evolution, and time-dependent strengthening at individual contacts.
	Identification of the onset of adhesion and irreversible contact strengthening as a function of RH and temperature, enabling direct comparison with bulk stickiness or T_g values obtained from DVS and DSC.
	Comparison of crystalline, amorphous, and mixed lactose contacts.
Outcome	Direct quantitative insight into how environmental conditions and phase state govern interparticle adhesion in lactose powders.

WP 3: Solid Bridge Formation and Aging in Lactose-Based Systems	
Aim	To elucidate mechanisms and time evolution of solid bridge formation in lactose powders.
Task	Time-resolved AFM experiments at constant load to monitor the development and aging of solid bridges between lactose particles.
	Identification of dominant mechanisms, including viscous flow of amorphous lactose, recrystallization-driven bridge formation, and surface restructuring.
	Microscopic imaging of contact regions and bridge morphology.
	Investigation of metastability and long-term evolution under sub-deliquescent humidity conditions.
Outcome	Mechanistic understanding of how solid bridges form and evolve in lactose powders over technologically relevant timescales.

WP 4: Bulk Rheology and Caking Behavior of Lactose Powders	
Aim	To link microscale contact mechanisms to macroscopic caking and flow behavior.
Task	Rheological characterization of lactose powders (flowability, yield stress, consolidation, creep) under controlled humidity and temperature.
	Stickiness and caking characterization using industrially relevant dynamic methods, such as rotating drum and/or fluidized bed tests under controlled humidity and temperature.
	Comparison of stickiness onset obtained from static (DVS, DSC) and dynamic (drum/fluid bed) bulk methods with microscale adhesion and contact evolution measured by AFM.
Outcome	Quantitative relationships linking single-contact physics to bulk caking behavior in lactose powders.

WP 5: Molecular Mobility and Water Distribution in Lactose Powders (NMR) in cooperation with TU Delft	
Aim	To probe molecular-scale dynamics governing moisture-mediated caking in lactose systems.
Task	NMR measurements to characterize water mobility and amorphous phase dynamics in lactose powders.
	Application to pure amorphous lactose, crystalline lactose, and mixed systems.
	Correlation of molecular mobility with AFM adhesion measurements and bulk caking strength.
Outcome	Molecular-level interpretation of caking mechanisms in lactose powders, strengthening the link between structure, dynamics, and mechanical behavior.

The planned Work Packages will be dealt in the following general time table:

Year	Main Focus	Active WPs
Year 1	Model systems & single-contact physics	WP1, WP2
Year 2	Bridge formation & bulk behavior	WP2, WP3, WP4
Year 3	Molecular dynamics & integration	WP3, WP4, WP5

5. Expected Results and Impact

Scientific Impact:

The proposed research will deliver fundamental advances in the understanding of powder caking mechanisms using lactose powders as a well-defined and industrially relevant model system. Lactose provides a unique platform due to the availability of crystalline and amorphous forms, its sensitivity to humidity and temperature, and its extensive prior use in caking studies, enabling direct comparison with existing theories and data. Specifically, the project is expected to:

- Resolve the disconnect between classical contact mechanics theories and experimentally observed caking behavior by providing direct, quantitative measurements of interparticle adhesion and irreversible contact formation under controlled temperature and humidity conditions.
- Establish, for the first time, a systematic and quantitative linkage between single-particle adhesion forces, solid bridge formation and time-dependent evolution, and macroscopic bulk behavior (flowability, yield stress, and consolidation) in lactose-based powders.
- Provide new mechanistic insight into the metastable nature of lactose caking, including the evolution of solid bridges formed by viscous flow of amorphous lactose, recrystallization processes, and moisture-mediated surface restructuring over extended storage times.
- Clarify the role of phase composition in mixed amorphous–crystalline lactose systems, addressing unresolved questions regarding the interaction between phases and their combined influence on caking kinetics and strength development.

Methodological Impact:

In addition to its scientific contributions, the project will establish a robust and transferable experimental methodology using lactose powders as a benchmark system. The expected methodological outcomes include:

- The development of a multi-scale experimental framework that integrates colloid probe atomic force microscopy, bulk powder rheology, and molecular-scale characterization techniques such as NMR, applied consistently to lactose powders under matched thermo-hygrometric conditions.
- Significant advancement of AFM colloid probe techniques through their systematic application to lactose particles under independently controlled humidity and temperature, enabling time-resolved investigation of adhesion, capillary condensation, viscous flow, and solid bridge formation at individual interparticle contacts.
- Demonstration of how microscale measurements obtained from lactose particles can be quantitatively upscaled to predict bulk caking behavior, establishing lactose as a reference material for future fundamental and applied studies on powder cohesion.

Industrial Relevance:

Lactose powders are widely used in the food and pharmaceutical industries, particularly as excipients in dry powder inhalers and tablet formulations, where caking and loss of flowability have direct implications for product quality and patient safety. The outcomes of this project will therefore have clear industrial relevance:

- Improved predictive capability for the caking propensity of lactose powders under realistic storage and handling conditions, reducing uncertainty in formulation and shelf-life assessment.
- Provide a mechanistic interpretation of widely used industrial stickiness and caking tests (DVS, rotating drum, fluid bed), enabling more informed use of these standard techniques without requiring their replacement by microscale methods.
- Mechanistically informed guidance for the rational design and stabilization of lactose-containing formulations, including control of amorphous content, moisture uptake, and particle-particle interactions.
- Broader relevance to other hygroscopic and partially amorphous powders, as the mechanistic insights and experimental framework developed using lactose can be transferred to chemically and physically related systems across the food, pharmaceutical, chemical, and materials sectors.

6. Critical Unknowns and Project Uncertainties

Despite extensive research on powder caking, several critical unknowns remain that may influence the direction and outcomes of this project.

1. The nature and reversibility of interparticle contacts in lactose powders under sub-deliquescent humidity and moderate temperature conditions are not well understood. It remains unclear when adhesion transitions from reversible to irreversible bonding, how strongly this transition depends on surface amorphous content, and whether repeated contact alters surface structure and contact mechanics.
2. The dominant mechanisms of solid bridge formation in lactose powders under storage-relevant conditions are unresolved. While viscous flow of amorphous lactose, moisture-induced recrystallization, and surface restructuring have all been proposed, their relative importance, possible coexistence, and time-dependent evolution remain unknown. The metastability and aging of solid bridges are particularly poorly understood.
3. The transferability of single-contact measurements to bulk caking behavior represents a key uncertainty. It is not yet clear how representative AFM colloid probe measurements are of the heterogeneous contact networks in bulk powders, or how microscale adhesion and bridge strength scale to macroscopic yield stress and flowability.
4. The role of phase distribution and molecular mobility in mixed amorphous-crystalline lactose systems remains largely unexplored. In particular, the relevance of NMR-derived measures of water mobility and amorphous phase dynamics for predicting mechanical caking behavior is not yet established.