BIORICH GROUP

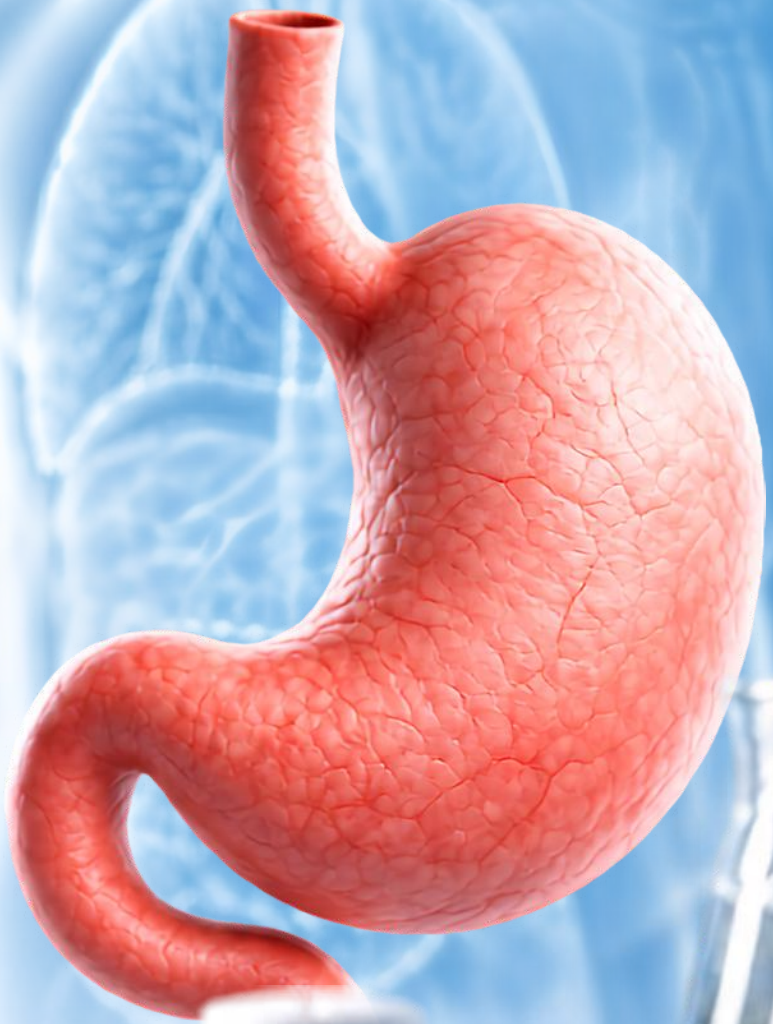
SEPTEMBER
09
2026

BIORICH
INSIGHTS

PHARMACEUTICAL INGREDIENTS, HEALTH SOLUTIONS & INNOVATION

DIGESTIVE FORMULATION TECHNOLOGY

FROM FORMULAR TO DIGESTIVE HEALTH SOLUTIONS



TABLET TECHNOLOGY
Optimizing processes and excipients to create quality tablets

ANTACID MEDICINE SOLUTIONS
Acid neutralization mechanisms and effective combination systems

HEALTH SUPPLEMENTS
Natural ingredients and probiotics supporting digestive health

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UNDERSTANDING FOR IMPROVED WELL-BEING

Delivering comprehensive insights into raw materials and solutions for the pharmaceutical sector.

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SCIENCE FOR HEALTH

QUALITY FOR LIFE

BIO RICH GROUP is a business operating in the field of supplying raw materials and biotechnology solutions to various industries.

We offer a wide range of products such as **active pharmaceutical ingredients (APIs), excipients, enzymes, vitamins, and other biological components**, serving the pharmaceutical, nutritional, healthcare, cosmetic, agricultural, and environmental industries.

PREMIUM QUALITY

We are committed to strict quality and safety standards for all our products.

SCIENCE-BASED SOLUTIONS

Driven by science and innovation to support pharmaceutical /food/cosmetic formulation for your business.

YOUR TRUSTED PARTNER

Building sustainable value through superior and reliable raw material products.

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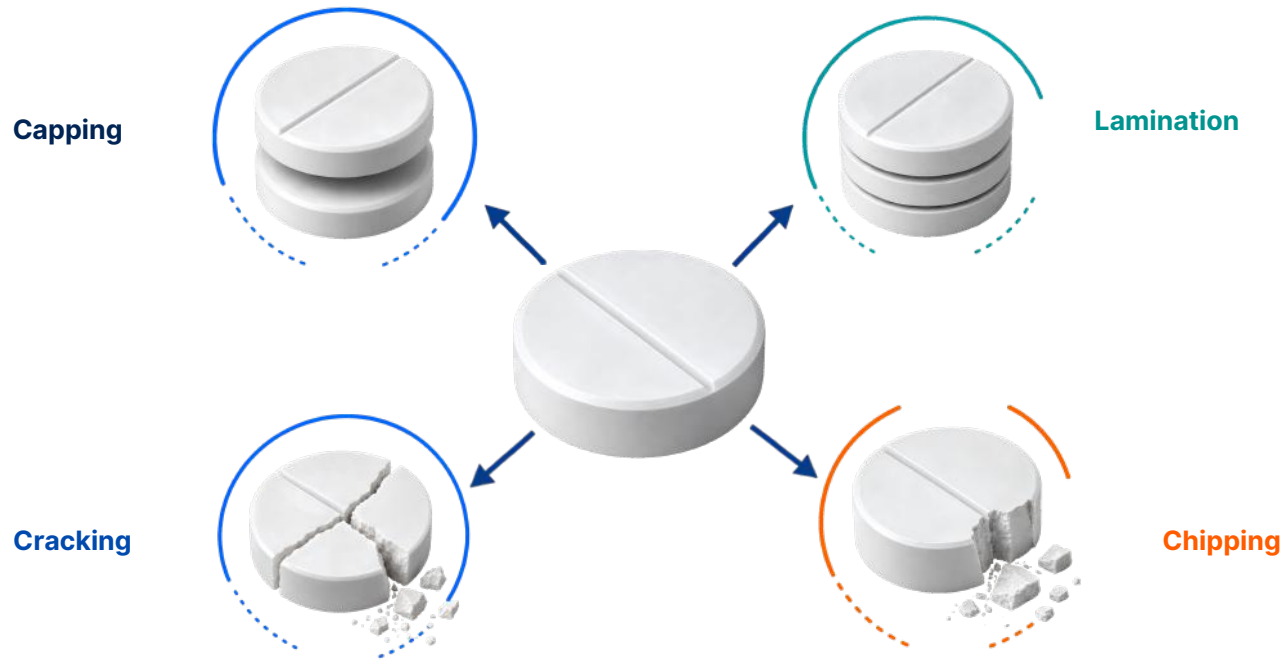
CAPPING LAMINATION CRACKING CHIPPING

STRUCTURAL DEFECTS IN TABLETS



MAINTAINING TABLET INTEGRITY

QUALITY
consistent & dependable

EFFICIENCY
Production optimization

SAFE
Minimize fundamental product risks.

EFFECTIVE
Enhance efficiency and minimize waste.

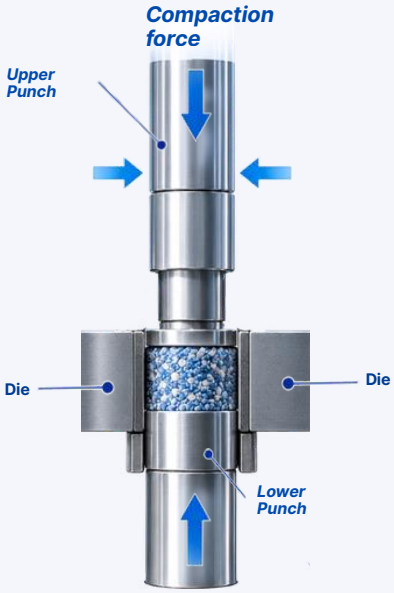
1 INTRODUCE

During compaction, the powder does not merely undergo "compressed into shape." Under the force of the punch and die, the powder bed undergoes a sequence of particle rearrangement, deformation, consolidation, and interparticle bonding to form the tablet structure.

STAGE 1: DIE FILLING

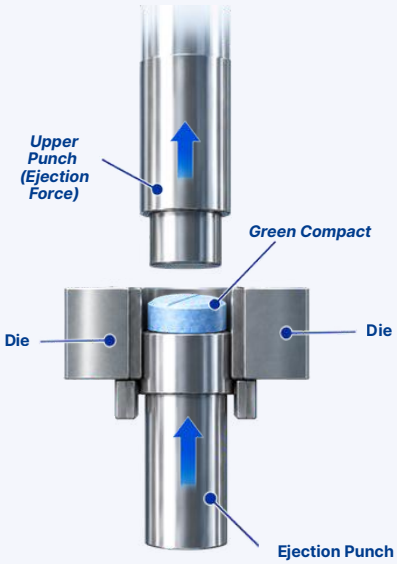
Loose powder is fed into the die cavity via a fill shoe

STAGE 2: COMPRESSION



Pressure is applied by upper and lower punches to compresses the powder into a green compact

STAGE 3: EJECTION



The lower punch expels the compressed mass from the die.

CHIPPING | CRACKING | CAPPING | LAMINATION

Changes occurring during the late compression and early ejection stages can impose mechanical stresses on the formed tablet structure, affecting its ability to maintain structural integrity. Structural failure may manifest as various types of defects, including capping, lamination, cracking, and chipping.

2 DEFINITION AND MECHANISMS OF DEFECTS

A. DEFINITION

01 CAPPING AND LAMINATING

- **Definition: Capping** is the partial or complete separation of the upper or lower crown from the main tablet body.
- **Definition: Lamination** is the separation of a tablet into two or more layers, forming interfaces that are approximately parallel to the tablet surface.

02 CRACKING

- **Definition: Cracking** is the formation of cracks on the surface or within the tablet structure, disrupting structural continuity without resulting in complete separation into distinct parts.

03 CHIPPING

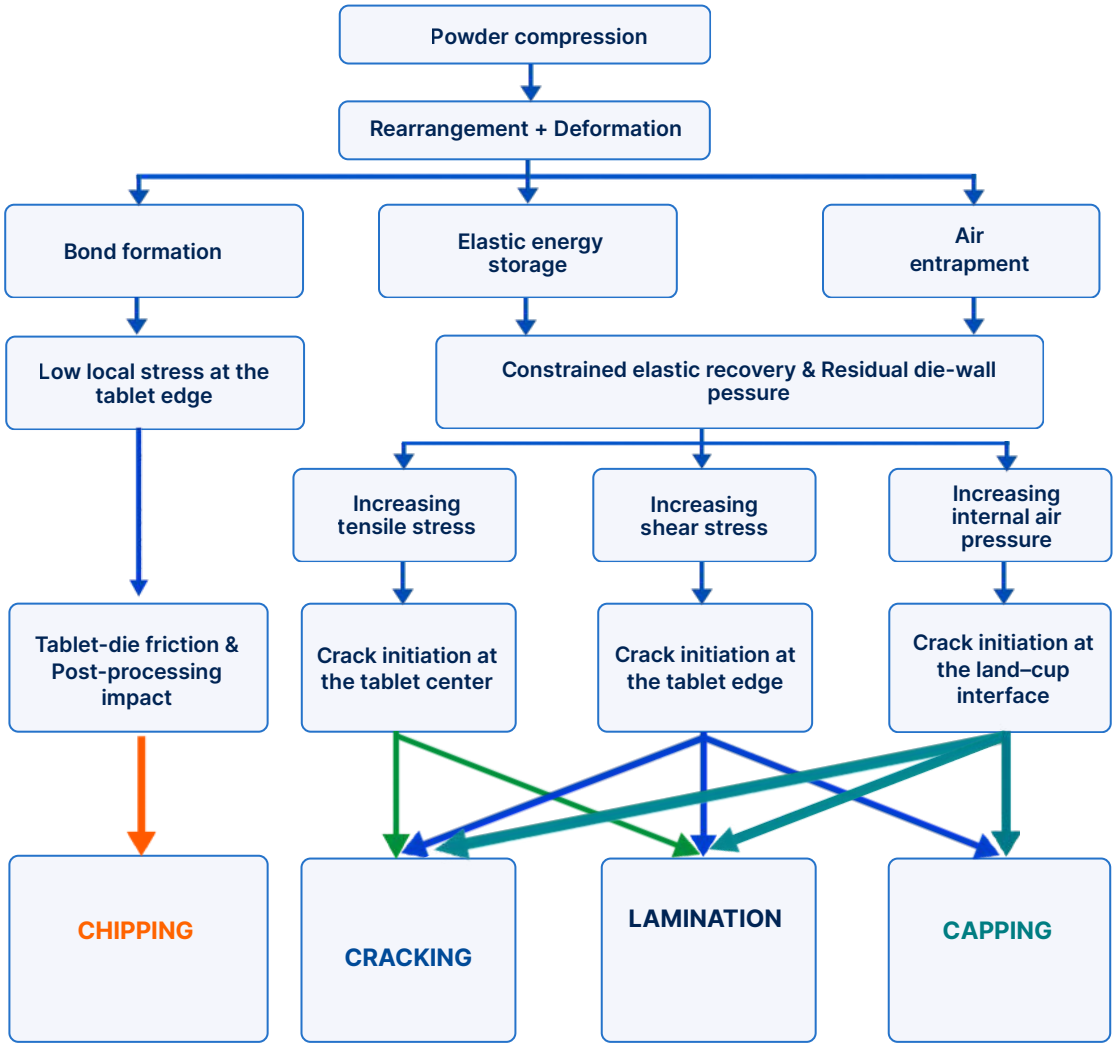
- **Definition: Chipping** is the detachment of a small portion of material from the tablet edge or upper crown surface, resulting in a chipped area.

B. MECHANISM

Compression Stage

Late Compression Stage

Ejection Stage



3 CAUSES OF TABLET DEFECTS

DEFECT	GRANULES	FORMULATION	PROCESSING	TABLETING PARAMETERS	TOOLING
CAPPING LAMINATION	• Excessive fines • Over-dried granules • Highly porous granules • Poor compactability • Non-uniform granules • Broad particle size distribution (PSD)	• Poorly compactable API • Insufficient binder • Poorly compactable filler • Imbalanced brittle-to-plastic excipient ratio • High total powder load (direct compression) • Excessive or insufficient lubricant	• Granulation method • Granulating liquid amount • Wet massing time • Impeller and chopper speed • Over-drying • Over-milling (milling speed and screen size). • Prolonged lubrication time • Prolonged or improperly sealed granule storage, leading to changes in granule structure and moisture content	• Excessive tableting speed • Insufficient dwell time • Excessive compression force • No pre-compression or ineffective pre-compression • Excessive fill depth • An excessively steep cam profile, resulting in high ejection force and high tablet ejection speed	• Inappropriate punch design (excessive cup depth, overly deep embossing, sharp-edged punch profile, etc.) • Uneven punch length • Worn, scratched, or uneven die surface • Insufficient lower punch height above the turret • Tablet collection tray positioned too low
CRACKING	• Excessively low or high moisture content • Non-uniform moisture content • Overly hard granules • Irregular rice flakes • Broad PSD, prone to segregation • Oversized granules • Excessive fines • Highly porous granules • Poor compactability	• Poorly compactable API • Poorly compactable filler • Insufficient binder • Excessive binder • Excessive lubricant migration • Insufficient plastic deformation excipient • Insufficient lubricant	• Granulating liquid amount • Wet massing time • Impeller and chopper speed • Inappropriate drying conditions, resulting in excessively low or high moisture content • Inappropriate screen size and milling speed, resulting in an unsuitable particle size distribution (PSD)	• Insufficient or excessive compression force • Excessive fill depth • No pre-compression or ineffective pre-compression • Excessive tableting speed • Insufficient dwell time	• Worn, scratched, or uneven die surface • Inappropriate punch design (overly deep embossing, sharp-edged punch profile, etc.) • Uneven punch length • Tablet collection tray positioned too low
CHIPPING	• Excessively low or high moisture content • Non-uniform moisture content • Poor compactability	• Insufficient binder • Poorly compactable filler • Poorly compactable API • Insufficient plastically deforming excipient and excessive brittle excipient	• Insufficient granulating liquid • Insufficient wet massing time • Inappropriate drying conditions • Inappropriate milling parameters and screen size, resulting in a broad particle size distribution (PSD)	• Excessive tableting speed • Insufficient dwell time • Low tablet collection tray • Lower punch below the turret during tablet ejection	• Inappropriate punch and die design (angles/edges, etc.)

4 CORRECTIVE APPROACH: ROOT CAUSE PRIORITY MATRIX

The priority matrix helps determine the order in which factors should be investigated to identify the root cause quickly and efficiently.

PHENOMENA	POWDER & GRANULE PROPERTIES	RECIPE	PROCEDURE	COMPRESSION SPECIFICATIONS	MORTAR AND PESTLE
 CAPPING	2	3	1	1	3
 LAMINATION	2	3	1	1	3
 CRACKING	1	1	2	3	2
 CHIPPING	2	3	2	1	1

1 First check 2 Next check 3 Later check

STICKING PICKING BINDING

MECHANISM OF DEFECT FORMATION

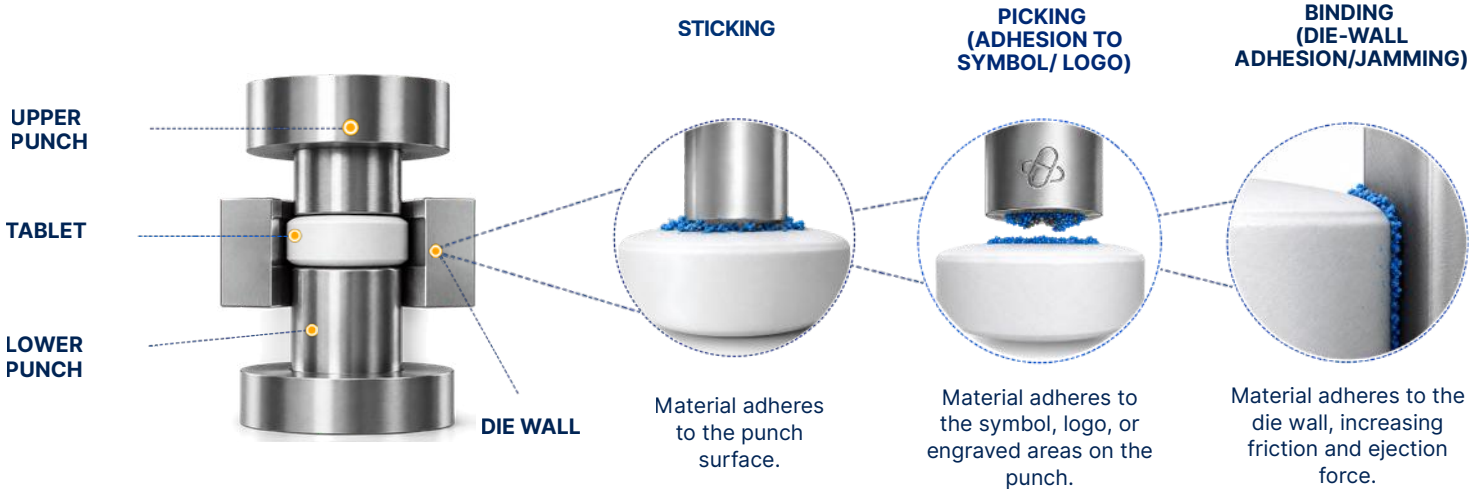
During tablet compression, tablet quality is determined not only by the formulation and the properties of the granules.

At the point when the tablet is compressed and subsequently separated from the punches and die, other factors also play a critical role in governing the interaction between the tablet and the tooling.

When these interactions are not adequately controlled, the material may adhere to the punch surface, accumulate in the engraved logo or lettering, or generate excessive friction against the die wall, resulting in familiar tableting defects such as **sticking**, **picking**, and **binding**.

1 TABLET–TOOLING INTERACTION AND DEFECT FORMATION DURING TABLETING

These three phenomena are often regarded as distinct defects. However, from a mechanistic perspective, they share a common feature, the interaction between the tablet and the tooling **(Tablet ⇔ Tooling)**



The issue is not simply a lack of lubricant. Rather, what is altering the balance among **adhesion**, **cohesion**, and **friction** during compression, decompression, and tablet ejection?

2 DEFINITION AND MECHANISMS OF DEFECTS

A. DEFINITION

01 STICKING

Sticking is the phenomenon in which **a portion** of the tablet **material adheres to the punch surface** during compression and punch withdrawal from the tablet, affecting the tablet surface, morphological uniformity, or tablet shape.

02 PICKING

Picking is a specific form of sticking in which **adhered material** is pulled away from the tablet at r**ecessed areas** or engraved features on the punch face, such as l**ogos, lettering, or symbols**. Due to the localized contact area and geometry of the engraved features, adhesion may become concentrated at these locations, resulting in material loss and defects in the corresponding surface details of the tablet.

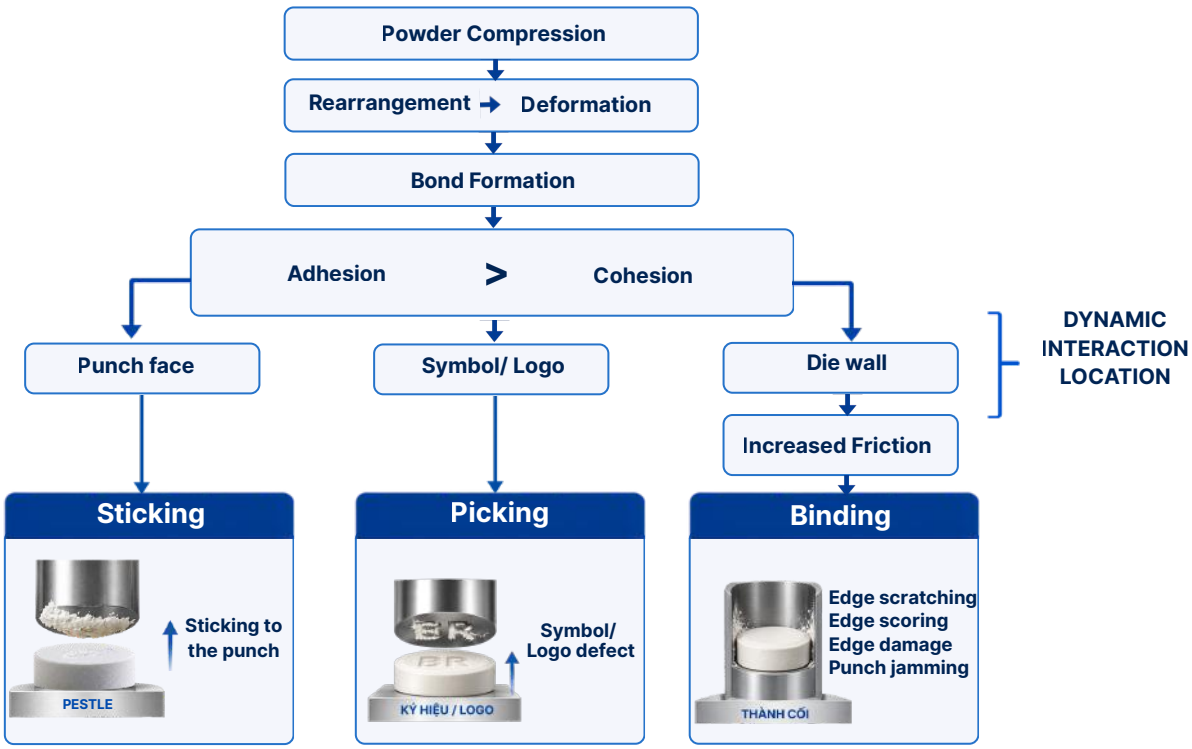
03 BINDING

Binding is the phenomenon in which **tablet material adheres to the die wall** during tableting, increasing friction as the tablet is ejected from the die. This phenomenon may increase ejection force and cause defects on the side surface or edge of the tablet.

B. MECHANISM

Compression Stage

Ejection Stage



When the balance among adhesion, cohesion, and friction is disrupted, defects such as sticking, picking, and binding may occur during compression, decompression, and tablet ejection.

3 CAUSES OF TABLET DEFECTS

DEFECT	GRANULES	FORMULATION	PROCESSING	TABLETING PARAMETERS	TOOLING	ENVIRONMENT
STICKING & PICKING	• Excessively moist granules • Excessive fines smooth. • Non-uniform granule moisture • Non-uniform lubricant distribution • Non-uniform binder distribution	• Insufficient lubricant • Inappropriate lubricant • Excessive binder or adhesive excipient • Insufficient binder resulting in excessive fines • Presence of low-melting-point components • Presence of highly hygroscopic components	• Insufficient drying, resulting in excessive residual moisture in the granules • Excessive fines due to granulation conditions (insufficient wet massing, insufficient or excessive granulating liquid, kneader speed, wet mill speed, sieve size, etc.) • Oversized granules causing residual moisture to remain trapped within the granules	• Low compression force, increasing the tendency for sticking • Low tableting speed • Excessive tablet press temperature • Inappropriate pre-compression settings	• Worn punch faces with loss of smoothness, pitting, or scratching • Inappropriate logo design • Excessively concave punch face (prone to sticking at the center)	• High room humidity and temperature
BINDING	• Excessive fines, resulting in reduced lubricant effectiveness • Excessive granule moisture • Rapid moisture uptake by the granules • Non-uniform lubricant distribution	• Insufficient lubricant • Inappropriate lubricant • Excessive adhesive components • Insufficient anti-caking agent, resulting in increased moisture uptake by the granules • Excessive tablet thickness	• Insufficient drying of the granules • Excessive fines due to granulation conditions (insufficient wet massing, insufficient or excessive granulating liquid, kneader speed, wet mill speed, sieve size, etc.) • Non-uniform lubricant mixing	• Excessive fill depth • Excessive tablet hardness • Excessive pre-compression force • Excessive tableting speed, resulting in an excessively high ejection speed.	• Worn or scratched die bore • Deformed die	• High room humidity and temperature

4 SOLUTIONS FOR STICKING – PICKING – BINDING

A defect observed on a tablet is merely the endpoint of a chain of interactions and does not necessarily reflect the cause at the location where the defect is observed. Accurate identification of the root cause is therefore essential for implementing appropriate corrective actions, as well as for controlling and preventing recurrence during manufacturing.

Root causes can be identified using a phenomenon → cause matrix, with potential causes investigated in order of priority:

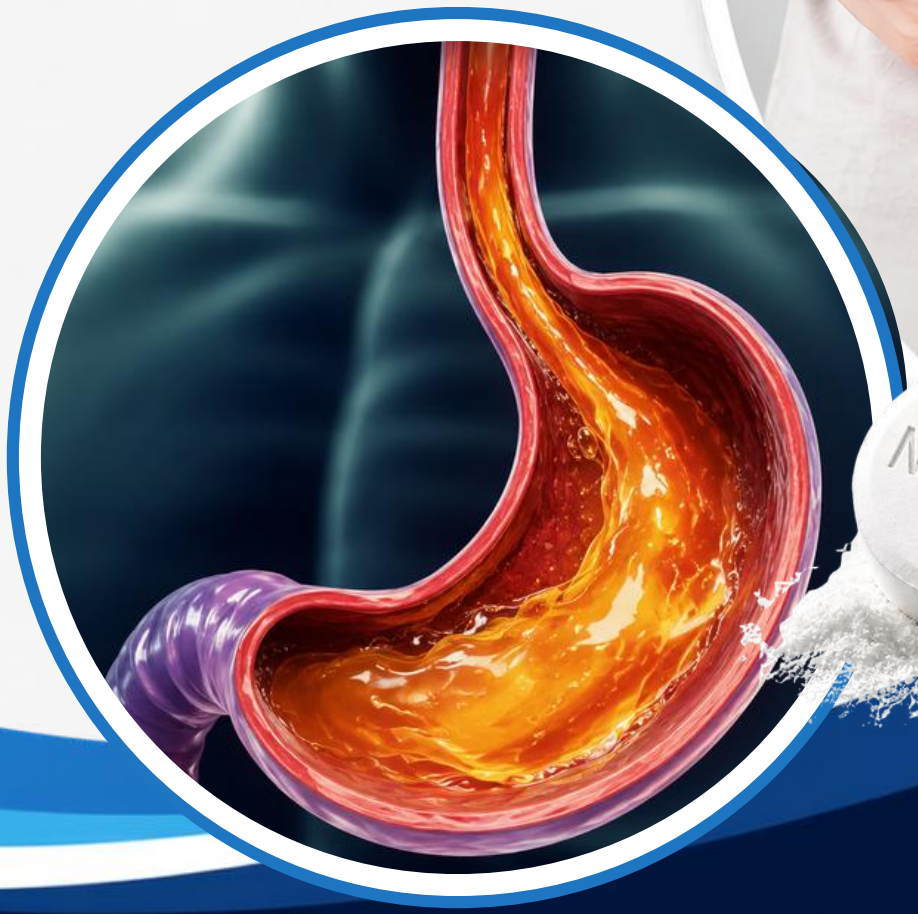
PHENOMENA	POWDER & GRANULE PROPERTIES	RECIPE	PROCEDURE	COMPRESSION SPECIFICATIONS	MORTAR AND PESTLE	ENVIRONMENT
 STICKING	1	1	2	3	1	1
 PICKING	1	1	2	3	1	1
 BINDING	1	1	2	1	1	3

1 First check 2 Next check 3 Later check

SODIUM BICARBONATE & CALCIUM CARBONATE

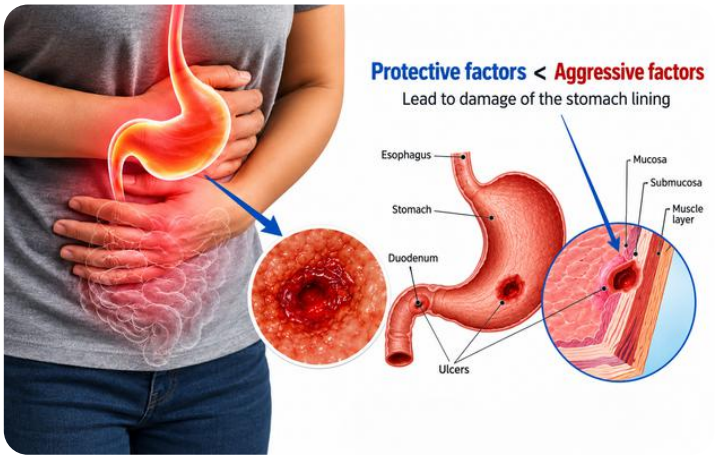
DIFFERENCES IN PRACTICAL APPLICATION

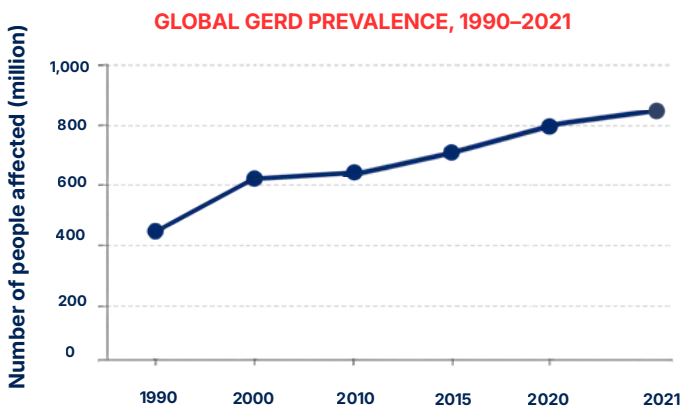
Both neutralize acid, yet differ in their properties, formulation behavior, and application value.



1 GASTROINTESTINAL DISEASE BURDEN & THE NEED FOR ACID CONTROL

Gastrointestinal diseases represent a significant global health burden, with **GERD** being one of the prominent conditions. Affecting hundreds of millions of people worldwide and increasing over recent decades, GERD creates a substantial need for symptom control, particularly rapid relief of heartburn and acid reflux.





Source: Global Burden of Disease (GBD) 2021

In this context, **Antacids** take a more direct approach by **neutralizing gastric acid**, thereby increasing **gastric pH** and supporting **rapid relief** of acid-related symptoms.

PROTECTIVE FACTORS
- Mucosal mucus layer
- Bicarbonate (HCO_3)

<

AGGRESSIVE FACTORS
- Gastric acid (HCl)
- Pepsin (protein-digesting enzyme)

2 PROPERTIES OF SODIUM BICARBONATE AND CALCIUM CARBONATE

Both serve as **Antacids**, but Sodium Bicarbonate and Calcium Carbonate differ in their physicochemical properties. These differences not only influence their acid-neutralizing capacity but also affect how each ingredient is selected and utilized in formulations.

CRITERIA	SODIUM BICARBONATE ($NAHCO_3$)	CALCIUM CARBONATE ($CACO_3$)
Main Role	Antacid	Antacid
Mechanism	$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$	$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$
Solubility	Souble in water (~ 90 mg/ml)	Practically insoluble in water
pH	8,3 (~ 0.8% w/v)	9,0 (10% w/v suspension)
Reaction rate (neutralization)	RAPID REACTION facilitating rapid acid neutralization	SLOWER REACTION THAN $NaHCO_3$ the reaction rate also depends on particle dissolution and surface area
Note	Excessive absorption of HCO_3^- may lead to metabolic alkalosis, while absorption of large amounts of Na^+ may worsen edema and congestive heart failure	Approximately 90% of the calcium chloride formed is converted into insoluble calcium salts or calcium soaps in the small intestine and is not absorbed. Calcium salts may cause constipation.
Other applications	• Alkalinizing agent • Effervescent agent	• Calcium source • Alkalinizing agent • Opacifying agent

3 APPLICATIONS OF SODIUM BICARBONATE AND CALCIUM CARBONATE

Sodium Bicarbonate and Calcium Carbonate are widely used in antacid products and various formulations due to their effective acid-neutralizing and pH-modifying properties.

A. APPLICATIONS IN ANTACID PRODUCTS

No.	PRODUCT	DOSAGE	ALGINIC ACID / SODIUM ALGINATE (mg/dose)	$NaHCO_3$ (mg/dose)	$CaCO_3$ (mg/dose)
1	 Antacid Tablets (USA)	2-4 tablets	-	-	500 - 1000
2	 Gaviscon Double Action (UK)	10 ml	500	213	325
3	 Gaviscon Tablets (It)	1-2 tablets	500	267	-
4	 Gaviscon Mint, tablet (Fr)	1-2 tablets	500	267	160
5	 Gavisconell (Fr)	1 pack	500	267	-

B. APPLICATIONS IN OTHER FORMULATIONS

01 Support Active Ingredient Stability

API: Omeprazole + Sodium Bicarbonate

$NaHCO_3$ serves as both an antacid and a means of reducing omeprazole degradation in the stomach. In addition, $NaHCO_3$ creates an alkaline microenvironment, helping to improve the stability of the formulation.

02 Support Active Ingredient Stability

API: Ertapenem sodium

Excipient: Sodium hydrogen carbonate

$NaHCO_3$ is used to control and adjust the pH of the formulation.

03 Support Active Ingredient Stability

API: Atorvastatin calcium trihydrate

Excipient: Calcium carbonate

$CaCO_3$ is used as an alkalizing agent and stabilizer, contributing to improved active ingredient stability.

04 Excipients utilized in effervescent systems

API: Paracetamol

Excipient: Sodium bicarbonate

$NaHCO_3$ is a component of the effervescent system and reacts with citr acid to generate CO_2. The molar ratio of citric acid to sodium bicarbona is 1:3.

05 Calcium sources

API: Calcium carbonate and Vitamin D_3.

$CaCO_3$ is used as a calcium source in calcium supplementation products.

ALUMINUM HYDROXIDE MAGNESIUM HYDROXIDE SIMETHICONE

COMPLEMENTARY MECHANISMS

& COMBINATION VALUE IN GI THERAPY

ACID CONTROL
Gastric acid neutralization

BALANCED ANTACID
Optimization of antacid profile

GAS RELIEF
Relief of flatulence, bloating, and eructation

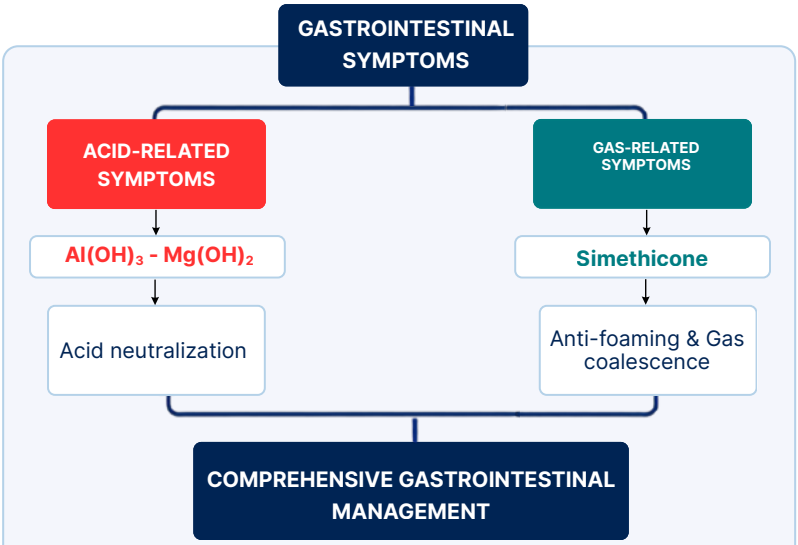
1 WHY CHOOSE THE $Al(OH)_3$ - $Mg(OH)_2$ & SIMETHICONE COMBINATION SYSTEM?

Gastrointestinal symptoms may involve multiple underlying mechanisms, among which **gastric acid** and the **presence of gas in the gastrointestinal tract** are two notable factors.

This provides a rationale for combining ingredients with different mechanisms of action within the same formulation system.

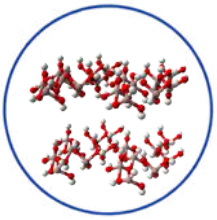
The value of a combination system lies not simply in using multiple active ingredients, but in the **complementarity of their mechanisms of action**.

THREE-COMPONENT COMBINATION SCHEME

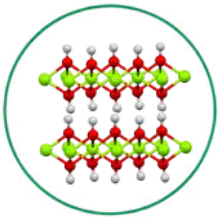


2 THE FIRST COMPLEMENTARY COMBINATION: $AL(OH)_3$ & $MG(OH)_2$

Aluminium Hydroxide and Magnesium Hydroxide are both antacids capable of neutralizing gastric acid. However, despite sharing the same therapeutic role, the two ingredients have different properties, providing a rationale for their combination within the same antacid formulation.



$Al(OH)_3$
Aluminium Hydroxide

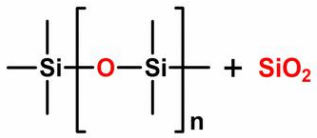


$Mg(OH)_2$
Magnesium Hydroxide

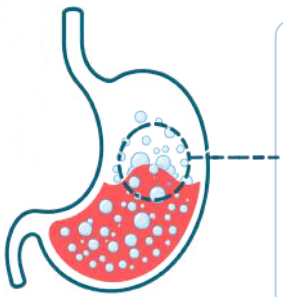
$Al(OH)_3$	CHARACTERISTIC	$Mg(OH)_2$
Relatively slow reaction rate	Reaction rate with HCl	Rapid reaction rate
Neutralization capacity varies with pH and environmental conditions	Acid neutralization capacity (ANC)	Achieves near total theoretical neutralization capacity within pH 1.0 - 4.5
Governed by reaction kinetics and gastric residence time	Time-dependent neutralization profile	Sustains neutralization under appropriate conditions, particularly postprandially (with food)
Tends to cause constipation	Effect on intestinal motility	Exhibits a laxative effect, potentially inducing diarrhea

COMBINING $AL(OH)_3$ & $MG(OH)_2$ → Complementary acid neutralization → Balanced impact on intestinal motility → MORE BALANCED ANTACID SYSTEM

3 THE NEXT COMPLEMENTARY COMBINATION: SIMETHICONE & ANTIFOAM ACTION

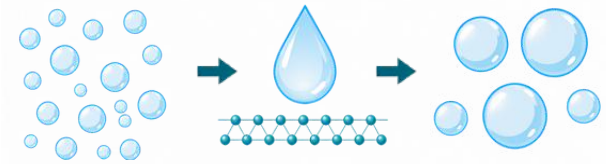


Gas in the gastrointestinal tract can originate from various sources, ranging from swallowed air to fermentation by the gut microbiota. When gas becomes trapped as gas bubbles or foam, Simethicone acts on their surface properties, facilitating the coalescence and release of gas for subsequent elimination.

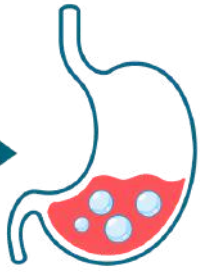


ENTRAPPED GAS
Causes flatulence and bloating

MECHANISM OF ACTION



SMALL GAS BUBBLES → SIMETHICONE (Reduces surface tension) → COALESCED GAS BUBBLES



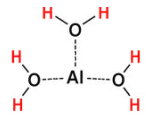
EASILY RELEASED GAS
Relieves flatulence and bloating

COMPLEMENTARY MECHANISMS OF ACTION → EXPANDING THE SPECTRUM OF SYMPTOM CONTROL FOR ENHANCED PATIENT COMFORT

4 FROM COMPLEMENTARY MECHANISMS TO COMBINATION VALUE

The combination of $Al(OH)_3$, $Mg(OH)_2$, and Simethicone is more than simply bringing multiple active ingredients together in a single formulation. Each component fulfills a distinct role, while their mechanisms provide complementary effects across the overall system.

Al(OH)3



ANTACID

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GASTRIC ACID NEUTRALIZATION

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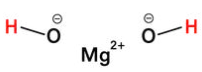
COMPLEMENTARY ANTACID OPTIMIZATION

Mg(OH)2



ANTACID

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GASTRIC ACID NEUTRALIZATION

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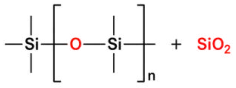
ANTACID PROFILE OPTIMIZATION

Simethicone



ANTI-FOAMING AGENT

↓

ACTION ON GAS BUBBLES & FOAM

↓

ADDED MECHANISM OF ACTION

EXPANDING THE SPECTRUM OF SYMPTOM CONTROL

- Gastric acid control
- Relief of flatulence - bloating - acid belching
- Enhanced patient comfort

VALUE OF THE COMBINATION SYSTEM

The value of this combination lies in the functional specialization and synergy of its ingredient, not merely in combining multiple actives. It broadens therapeutic coverage across gastrointestinal symptoms toward a unified target.

> **PROVIDING GREATER PATIENT COMFORT**

A COMBINATION IS VALUABLE ONLY WHEN INGREDIENTS DO NOT MERELY COEXIST IN A FORMULATION, BUT ACTIVELY COMPLEMENT EACH OTHER FUNCTIONALLY.

5 MARKET APPLICATIONS

$Al(OH)_3 + Mg(OH)_2$	$Al(OH)_3 + Mg(OH)_2$ + Simethicone	$CaCO_3 + Mg(OH)_2$ + Simethicone
ANTACID	**ANTACID + GAS RELIEF**	**ANTACID + GAS RELIEF**

Maalox®

Oral Suspension
Each 5 mL includes:

- Magnesium hydroxide **200 mg**
- Aluminum hydroxide **175 mg**

Maalox Plus

Oral Suspension
Each 5 mL includes:

- Magnesium hydroxide **200 mg**
- Aluminum hydroxide **175 mg**
- Simethicone **25 mg**

Mylanta® 1

Chewable Tablet
Each tablet includes:

- Calcium carbonate **1000 mg**
- Magnesium hydroxide **270 mg**
- Simethicone **80 mg**

DIBASIC CALCIUM PHOSPHATE

ANHYDROUS & DIHYDRATE

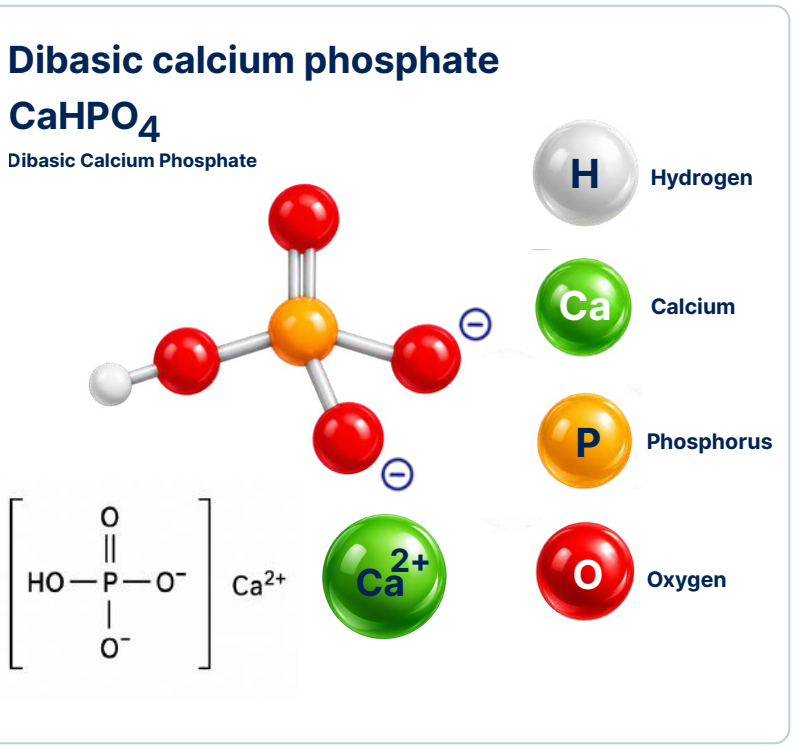
TECHNOLOGICAL DIFFERENCES IN FORMULATION DESIGN

> BOTH ARE DIBASIC CALCIUM PHOSPHATE
> HOWEVER, THEY ARE NOT ENTIRELY THE SAME IN TERMS OF TECHNOLOGY.

1 INTRODUCE

What has made **Dibasic Calcium Phosphate (DCP)** widely used in pharmaceuticals for more than half a century is not simply its role as a diluent, but its unique combination of properties that few other excipients can offer in a single material. Its **fragmentation-based compaction**, **low hygroscopicity**, **chemical inertness**, and **good flowability** (in granular grades) have made DCP a familiar choice in many tablet formulations, particularly direct-compression systems.

However, not all Dibasic Calcium Phosphate materials exhibit the same technological properties. **Differences in the hydration state** alone can lead to **significant changes in the material's technological performance**. This is why DCP Anhydrous and DCP Dihydrate cannot always be used interchangeably during formulation development, despite both being referred to as Dibasic Calcium Phosphate.



2 BADVANTAGES OF DIBASIC CALCIUM PHOSPHATE

In essence, Dibasic Calcium Phosphate (DCP) is an inorganic calcium hydrogen phosphate salt, primarily used as a diluent in solid dosage forms. Unlike organic diluents, DCP possesses several key characteristics that distinguish it, including:

01

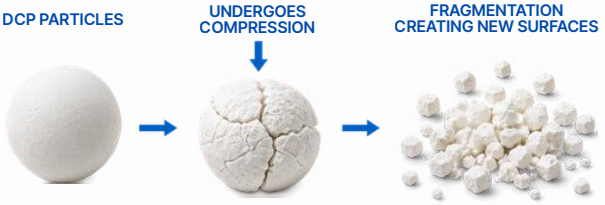
DIRECT COMPRESSION & COST EFFICIENCY

Unlike many direct-compression excipients, DCPD is widely favored for its **good flowability, low hygroscopicity,** and **low cost.**

02

COMPRESSION FRACTURE MECHANISM

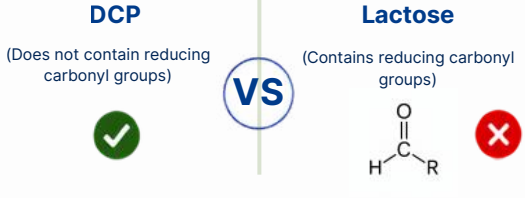
Under compression, DCP particles fracture into numerous smaller fragments, creating new surfaces. This characteristic makes DCP **less sensitive to over-lubrication** and **final blending parameters during scale-up.**



03

CHEMICAL INERTNESS

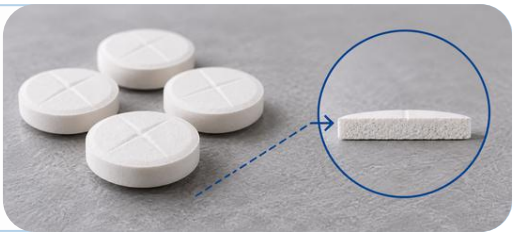
DDCP **does not contain reducing carbonyl groups**, thereby minimizing the risk of Maillard reactions—a major limitation associated with lactose.
In addition, DCP exhibits **very low hygroscopicity** compared with cellulose- and starch-based diluents.



04

HIGH DENSITY AND EXCELLENT FREE-FLOWING PROPERTIES (GRADE COARSE/UNMILLED)

In direct-compression formulations, DCP enables **tablet size optimization** for high-dose formulations while providing a basis for **shortening manufacturing time**.



3 DIBASIC CALCIUM PHOSPHATE GRADES

HYDRATION STATE	DIBASIC CALCIUM PHOSPHATE ANHYDROUS (DCPA) $CaHPO_4$	DIBASIC CALCIUM PHOSPHATE DIHYDRATE (DCPD) $CaHPO_4.2H_2O$
PARTICLE SIZE	There are two grades: powder and granular	There are two grades: powder and granular
MOLECULAR MASS	136.06 g/mol	172.09 g/mol
TRUE DENSITY	2.312 g/cm^3	2.959 g/cm^3
MELTING POINT	Does not melt; decomposes at approximately 425°C to form calcium pyrophosphate	Loses its water of crystallization below 100°C
HYGROSCOPICITY	Very low hygroscopicity	Very low hygroscopicity
SURFACE pH	Dependent on the manufacturing process: • Powder grades typically have a near-neutral pH • Granular grades typically have a pH of 5.0 – 6.0	Dependent on the manufacturing process: • Typically has a pH of 7.0 – 8.0
NOTE	The surface pH of powdered and granular DCPA differs, which should be considered when changing the manufacturing process for acid-sensitive active ingredients.	The surface pH of DCPD is mildly alkaline, so caution should be exercised when using it with alkali-sensitive active ingredients.

4 APPLICATIONS OF DIBASIC CALCIUM PHOSPHATE IN FORMULATIONS

Dibasic Calcium Phosphate is used as a diluent in pharmaceutical formulations.

APPLICATION	DCP GRADE	COMMONLY USED APIS
Direct compression with low cost and excellent flowability	• Granular DCPA • Granular DCPD	• Paracetamol • Chloroquine diphosphate • Clobazam
Amine-containing APIs	• The choice between DCPA and DCPD depends on the acid–base sensitivity of the active ingredient.	• Paroxetine • Diclofenac sodium • Ethambutol
Vitamins and multivitamins	• Granular DCPA • Granular DCPD	• Beta-Carotene • Vitamin A, D, E, C, B1, B2
APIs stable in weak bases and acid-sensitive	• Granular DCPD	• Desloratadine
APIs sensitive to moisture and/or stable in weak acids	• Granular DCPA	• Lisinopril • Sildenafil citrate

Selecting the appropriate DCPA or DCPD grade is critical to formulation performance and tablet quality.

MCC +
2% Colloidal
Silicon Dioxide

SILICIFIED MICROCRYSTALLINE CELLULOSE

Silicification as a solution to enhance technological properties

- IMPROVED FLOWABILITY
- ENHANCED COMPRESSIBILITY & PLASTIC DEFORMATION
- REDUCED SENSITIVITY TO LUBRICANTS
- OPTIMIZED FOR DIRECT COMPRESSION

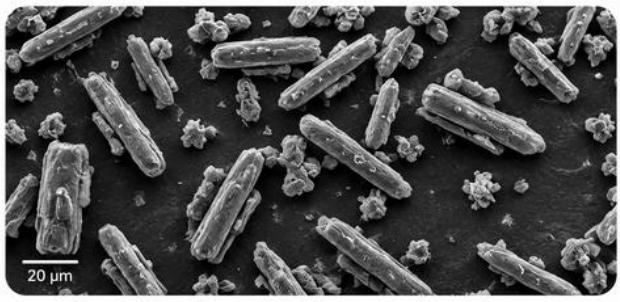
1 THE DEVELOPMENT OF SILICIFIED MICROCRYSTALLINE CELLULOSE (SMCC)

Microcrystalline Cellulose (MCC) is one of the most widely used excipients in tablet formulations, particularly for **direct compression**, owing to its **good plastic deformation and compressibility**, which support the formation of tablets with high mechanical strength.

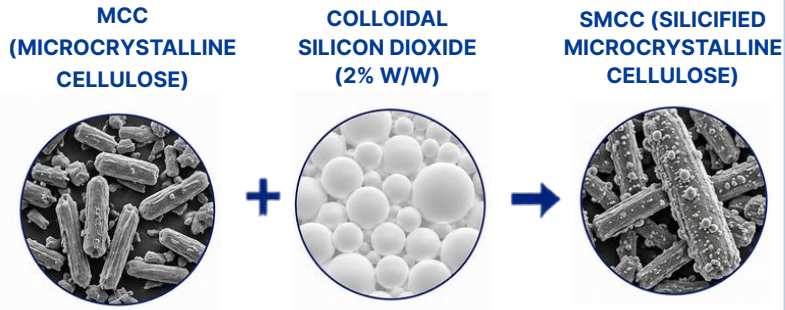
However, **MCC** has some limitations, including **suboptimal flowability, low bulk density**, and **sensitivity to moisture and lubricants**, which may affect tablet performance and quality.

THE ISSUE IS:

Can the technological properties of MCC be improved while maintaining its inherent advantages?



20 µm SEM image of HiCel™ SMCC (Silicified Microcrystalline Cellulose)



SILICIFICATION PROCESS

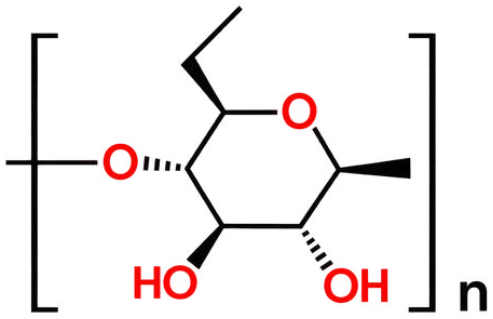
MCC is silicified with Colloidal Silicon Dioxide to enhance its technological properties

- IMPROVED FLOWABILITY
- INCREASED BULK DENSITY
- REDUCED SENSITIVITY TO LUBRICANTS
- MAINTAINED GOOD PLASTIC DEFORMATION & COMPRESSIBILITY

SMCC is not merely a physical blend of MCC and Colloidal Silicon Dioxide, but the product of a silicification process designed to optimize the material's technological properties.

2 PROPERTIES OF SMCC

CHEMICAL STRUCTURE

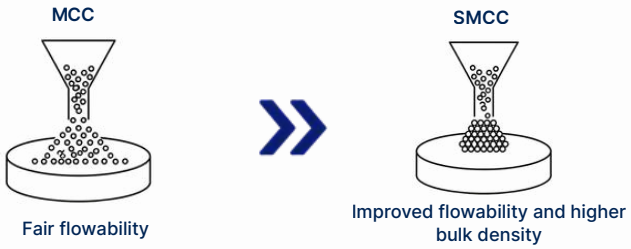


- **Co-processed material** consisting of **MCC and 2% w/w colloidal silicon dioxide**; silicification does not result in significant chemical modification or polymorphic transformation
- Relatively **chemically inert**
- **Insoluble in water**, but retains **water sorption and swelling** properties similar to MCC
- **Improved flowability**, making it suitable for various direct-compression formulations
- **Better compressibility than MCC**
- Exhibits **plastic deformation behavior**
- **Reduced sensitivity to lubricants** (magnesium stearate) compared with MCC of similar mean particle size
- Like MCC, SMCC is available in **various particle sizes and bulk densities**, allowing its use across different formulation and manufacturing processes.

3 ADVANTAGES OF SMCC

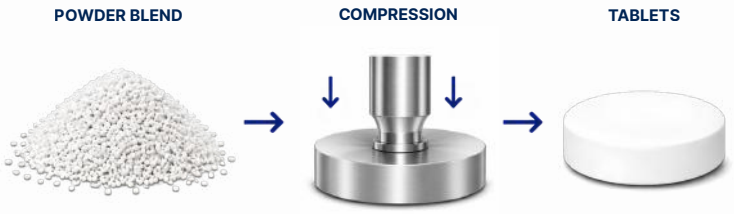
01 IMPROVED FLOWABILITY

SMCC exhibits superior flowability and higher bulk density compared to standard MCC. This enhances powder flow and ensures more consistent die filling, which is particularly beneficial for direct compression formulations.



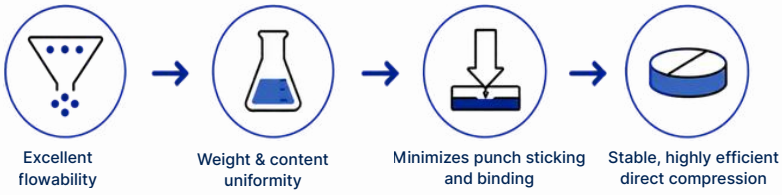
02 SUPERIOR COMPRESSIBILITY & TABLETABILITY

SMCC retains the plastic deformation capability and interparticle bonding mechanism inherent to the MCC matrix, while offering exceptional compressibility to support the production of tablets with high mechanical strength



03 DIRECT COMPRESSION PROCESS OPTIMIZATION

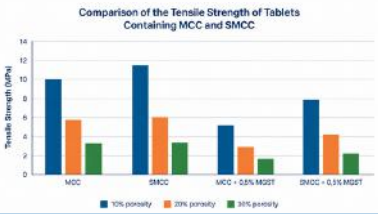
Minimizes punch sticking and capping, prevents powder blend segregation, and ensures weight and content uniformity-especially effective for low-dose or difficult-to-compress active pharmaceutical ingredients (APIs).



04 REDUCED LUBRICANT SENSITIVITY

In a comparative study, SMCC demonstrated lower loss of tablet mechanical strength than MCC (of equivalent mean particle size) in the presence of magnesium stearate, highlighting its ability to maintain superior tabletability upon lubrication.

EFFECT OF MAGNESIUM STEARATE ON TABLET MECHANICAL STRENGTH



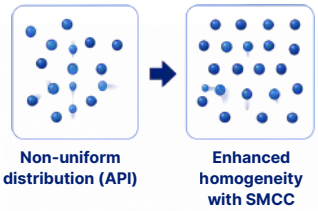
SMCC maintains better mechanical strength than MCC in the presence of magnesium stearate.

4 APPLICATIONS AND ROLE OF SMCC IN PHARMACEUTICAL FORMULATION

01 HIGH-DOSE API FORMULATIONS

High API loading can alter the flow characteristics and compactibility of the powder blend → SMCC serves as a **binder-filler**, enhancing the **flowability** and **tabletability** of the system.

02 FORMULATIONS REQUIRING HOMOGENEITY CONTROL



Non-uniform API distribution within the blend can compromise tablet content uniformity → leveraging its **flow properties** and **porous micro-structure**, SMCC helps achieve a more homogeneous powder blend.

03 FORMULATIONS REQUIRING EXCELLENT TABLETABILITY

Achieving target mechanical strength without applying excessive compression forces → SMCC's **high compressibility** and **plastic deformation** facilitate the production of tablets with adequate mechanical strength at lower compression forces.

04 FORMULATIONS PRONE TO PUNCH STICKING

SMCC helps maintain a clean punch surface and **minimizes punch sticking** compared to MCC and physical blends of MCC/Silica in specific formulations.

4 APPLICATION & ROLE OF SMCC IN FORMULATION (CONTINUED)

FORMULATION RESEARCH STUDIES OF SMCC

ACTIVE INGREDIENT – DOSE	DOSAGE FORM	SMCC USAGE (%)	PURPOSE
Levothyroxine – 0.025 mg *	Tablets	~94,2%	Used as the primary excipient at a high concentration. Thanks to its porous microstructure (2–3 µm), SMCC entraps and protects levothyroxine from degradation
Loratadine – 10 mg **	ODT	~15,7%	SMCC's asymmetric particle structure minimizes segregation and maintains blend uniformity. Its ability to achieve high tablet strength at low compression forces, combined with water-wicking, promotes rapid disintegration.
Simvastatin – 10 mg ***	ODT	~46,5%	Acts as a filler for ODTs, forming the primary matrix that enables ultra-fast disintegration (<30 seconds) and low friability (<0.2%).

NOTE: "*", "", and "***" are cited from patents US6399101B1, EP1773292B1, and WO2007020079A2, respectively.**

COMMERCIAL MARKET PRODUCTS UTILIZING SMCC

ICOTYDE®

Icotrokina – 20 mg

VORANIGO®

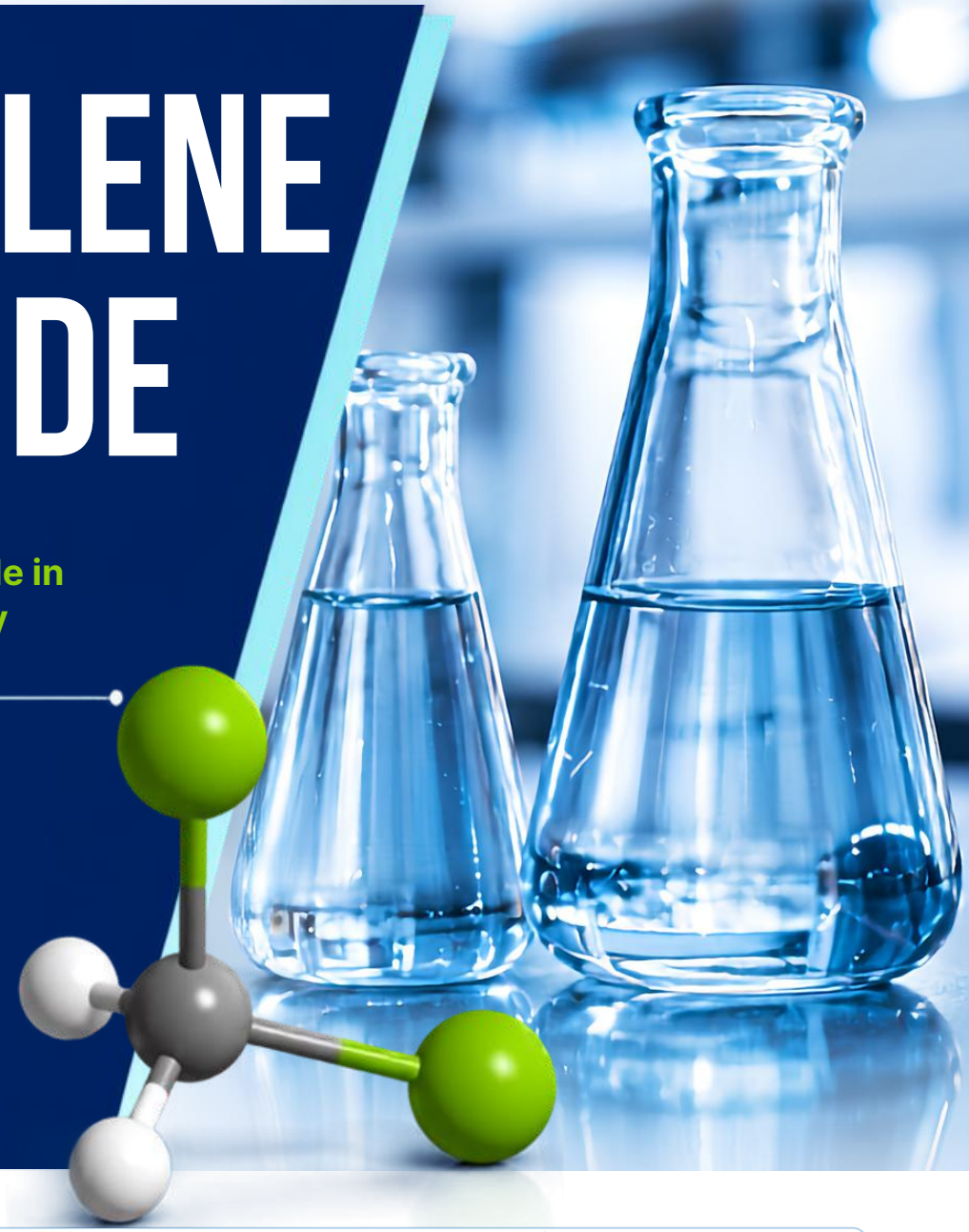
Voracidenib – 40 mg

ZURZUVAE®

Zuranolone – 25 mg

METHYLENE CHLORIDE

Organic solvents & their role in pharmaceutical technology



Methylene chloride, also known as Dichloromethane (DCM), is a halogenated compound with the molecular formula CH_2Cl_2 and CAS No. 75-09-2, belonging to the class of chlorinated solvents. It is a colorless, highly volatile liquid widely used as a solvent across various industries and manufacturing processes.

FORMULA	MOLECULAR WEIGHT	BOILING POINT	CAS NUMBER
CH_2Cl_2	84.93 g/mol	~ 40°C	75-09-2

VERSATILE SOLVENT

Dissolves a wide range of organic compounds, resins, and polymers.

WIDE APPLICATIONS

Used in extraction, film coating, active ingredient processing, and manufacturing.

COMPLIANT WITH STANDARDS

High purity – meets the requirements of multiple industries.

1 WHAT IS METHYLENE CHLORIDE?

DICHLOROMETHANE (DCM)

BEFORE 1840
CHEMICAL PREMISE

DCM was synthesized via the reduction of chloroform with zinc and hydrochloric acid in an alcoholic medium. However, the process was **complex**, **costly**, and **difficult to scale up** industrially.

1840
DISCOVERY

Henri Victor Regnault marked a milestone in the synthetic pathway of DCM when he first prepared DCM from methyl chloride through photochlorination.

1923
TURNING POINT

The **Farbwerke Hoechst** plant commercialized the methane chlorination process, marking a transition toward the **industrial production** of dichloromethane and trichloromethane.

LATE 20TH CENTURY
EXPANSION OF APPLICATIONS

Moving beyond industrial solvent applications, DCM expanded into pharmaceutical manufacturing, particularly in **extraction**, **purification**, and **film-coating solvent** processes requiring ultra-high purity standards.

PRESENT DAY
STRINGENT REGULATIONS

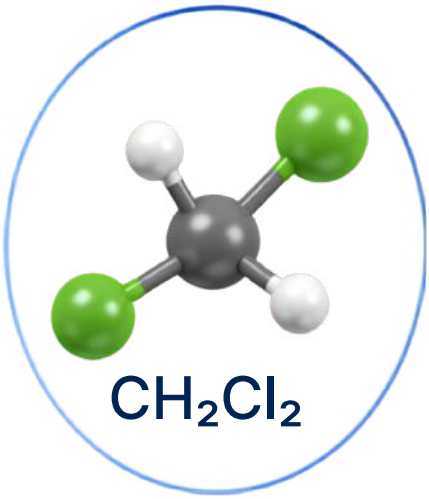
DCM is subject to strict **environmental**, **emission control**, and **occupational health** and **safety** regulations, leading to reduced consumption and lower production capacity. Nevertheless, DCM remains a widely used solvent due to specialized applications that cannot be easily substituted.

2 CHARACTERISTICS OF METHYLENE CHLORIDE

These essential properties play a significant role in the function of DCM across various industrial and pharmaceutical processes.

MOLECULAR FORMULA
CH_2Cl_2

MOLECULAR MASS
84,93 g/mol

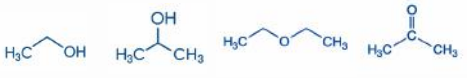


METHYLENE CHLORIDE

NATURE
- Colorless, transparent liquid
- Highly volatile (boiling point ~40°C)
- Low flammability compared with many other organic solvents

Colorless | Volatile (~40°C) | Low flammability

SOLUBILITY
Slightly soluble in water and miscible with many organic solvents, such as alcohols, ethers, and ketones



Ethanol | Isopropyl alcohol | Ether | Acetone

POLARITY
MEDIUM POLARITY

A **moderately polar organic solvent** that dissolves a wide range of organic compounds. Widely used in extraction, separation, and purification processes for medicinal materials and active pharmaceutical ingredients (APIs)

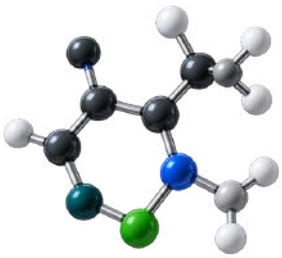
SAFETY PROFILE
Highly volatile, with potential for occupational exposure

QCVN 03:2019/BYT
Occupational exposure limit
50 mg/m^3
(TWA – 8 hours)

IARC CLASSIFICATION
GROUP 2A
Potential carcinogenic hazard to humans

3 BENEFITS OF METHYLENE CHLORIDE

01 EXCELLENT SOLUBILITY FOR VARIOUS ORGANIC COMPOUNDS



- **Dissolves a wide range of organic compounds**, resins, and **polymers**, particularly effective for materials with low to moderate polarity.
- Widely used in extraction, purification, and dissolution of organic compounds, moisture-protective polymers, enteric coating polymers, etc.

• EXTRACTION • PURIFICATION • POLYMER DISSOLUTION

02 HIGH EVAPORATION RATE

BOILING POINT
~40 °C

- **Easily removed from the system** following processing steps.
- Accelerates spray rate → **shortens coating process time** → reduces manufacturing costs.
- Low boiling point (~40 °C) → requires low coating temperatures → **minimizes degradation of heat-sensitive APIs**

03 HIGH MISCIBILITY WITH OTHER SOLVENTS

- Combines with **ethanol, isopropyl alcohol, and acetone** to form co-solvent systems.
- **Adjusts solubility profile and evaporation characteristics** as required.
- Easily dissolves **poorly soluble polymers or plasticizers**, such as cellulose acetate, hypromellose phthalate, dibutyl sebacate, etc.
- Modulates system polarity for **extraction and purification of APIs**, achieving high purity levels.

04 SUITABLE FOR WATER-SENSITIVE APIS

ORGANIC SOLVENT SYSTEM

- Enables the formulation of organic solvent systems, **minimizing the introduction of large amounts of water** into the process.
- Ideal for **moisture-sensitive active ingredients or formulation systems**, depending on process design.

4 USES OF METHYLENE CHLORIDE

Due to its properties that meet a variety of technological needs, DCM is selected as a solvent in numerous processes, including material dissolution and processing, extraction, film formation, and the production of industrial products.

01 PHARMACEUTICAL INDUSTRY

Primary solvent or co-solvent in film coating, extraction, and select active pharmaceutical ingredient (API) processing stages.

02 FOOD INDUSTRY

Applied in the extraction and purification of natural compounds derived from herbal materials.

03 CHEMICAL INDUSTRY

Solvent for extraction, separation, purification, and organic synthesis/reaction processes.

04 POLYMER & MATERIALS INDUSTRY

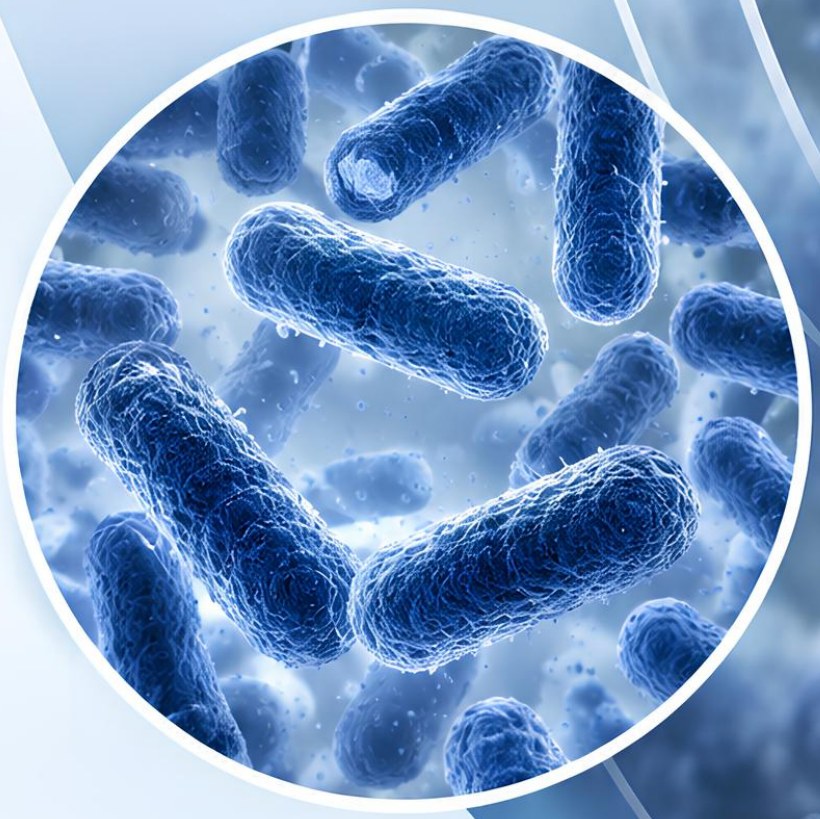
Used to dissolve and process polymers/resins, as well as in specific material manufacturing workflows.

05 COATINGS & PAINTS

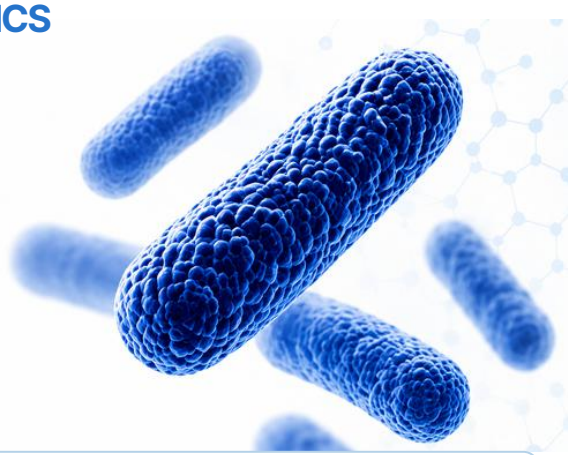
Utilized as a solvent in paint stripping formulations and select industrial coating systems.

BACILLUS CLAUSII & SUBTILIS

BIOLOGICAL CHARACTERISTICS & PROBIOTIC APPLICATIONS



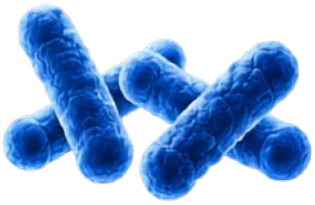
1 *BACILLUS* - OVERVIEW AND KEY CHARACTERISTICS



Bacillus is a genus of **Gram-positive, rod-shaped** bacteria characterized by their ability to form **endospores** under unfavorable conditions. The spores allow the bacteria to enter a dormant state, increasing their resistance to various environmental stresses. In the field of probiotics, ***B. clausii*** and ***B. subtilis*** are two notable representatives used in probiotic preparations for human use.

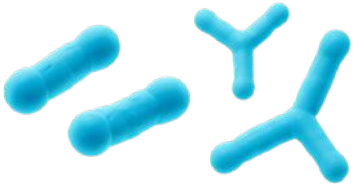
The key distinction of Bacillus does not lie in being "***better probiotics***," but in its **ability to form spores**. While many probiotics such as ***Lactobacillus*** and ***Bifidobacterium*** are primarily used in the form of **vegetative cells**, Bacillus can transition into a spore form with **high resistance to various physical and chemical stresses**, providing an important technological advantage for the development and preservation of probiotic preparations.

BACILLUS



- Gram positive
- Rod shape
- Endospore development

LACTOBACILLUS BIFIDOBACTERIUM



- Gram positive
- Rod-shaped or branched
- Primarily used in the form of vegetative cells

KEY ADVANTAGE

ABILITY TO FORM ENDOSPORES

PROVIDES ENHANCED RESISTANCE TO VARIOUS ENVIRONMENTAL STRESSES

2 *BACILLUS* - ACTIVE STATE & "DORMANCY"

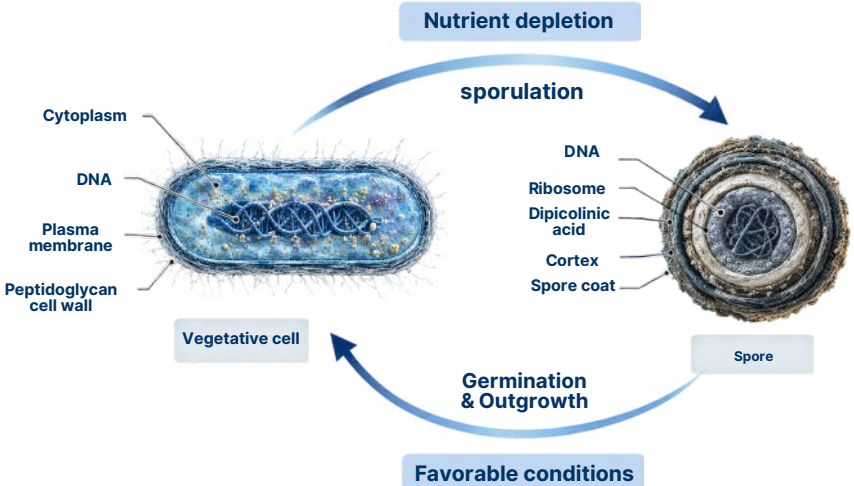
Bacillus can alternate between an **active state (vegetative cell)** and a **dormant state (endospore)** based on environmental conditions.

01 NUTRIENT DEPLETION → SPORULATION

When nutrient availability declines, vegetative cells of Bacillus can activate a differentiation program known as **sporulation**. The cell forms an asymmetric septum, producing a **forespore** and a **mother cell**. The mother cell surrounds and coordinates the maturation of the forespore, forming the **cortex, spore coat**, and other internal protective mechanisms, before eventually lysing and releasing the **mature endospore**.

02 FAVORABLE CONDITIONS → GERMINATION

When favorable conditions return, the endospore **senses environmental signals** and initiates **germination**. This process involves the release of **Ca-DPA**, cortex degradation, and rehydration of the spore core, occurring **within minutes**. Metabolic activity is restored, after which the spore develops into a **vegetative cell** capable of growth and division.



Spore resistance to environmental stresses


High temperature


Desiccation


UV exposure


Chemical stress


Gastric acid/ Bile salts

3 *B. CLAUSII & B. SUBTILIS:* SIMILARITIES AND DIFFERENCES

NOTE

The ability to form endospores is a **general characteristic of the species**, whereas **stress resistance, germination, and biological activities may vary among strains.**

CHARACTERISTIC	*B. SUBTILIS*	*B. CLAUSII*
Structural characteristics	Gram-positive, rod-shaped bacterium capable of forming endospores	Gram-positive, rod-shaped bacterium capable of forming endospores
Spore stability	Multilayered spore structure enhances resistance to heat, drying, UV, and other environmental stresses	Spores exhibit resistance to heat, acid, and gastrointestinal (GI) conditions
Antibiotic resistance	Antibiotic resistance profiles are strain-dependent and should not be generalized to the species	Some strains exhibit multidrug-resistant phenotypes; resistance mechanisms in probiotic strains have been investigated as stable genetic traits, but remain strain-specific
Antimicrobial activity	Capable of producing diverse secondary metabolites such as surfactin, plipastatin, and bacillaene	Some strains can produce clausin and other antimicrobial substances, mainly reported against certain Gram-positive bacteria
Biological characteristics	Produces a broad range of extracellular enzymes, including proteases, amylases, and xylanases, and exhibits diverse secondary metabolism	Some strains exhibit mucosal adhesion, β-galactosidase production, and production of certain B vitamins
Clinical evidence	Human clinical evidence is primarily concentrated on specific strains, such as BS50, DE111, and R0179	Has a longer history of clinical use and research, particularly for B. clausii-containing preparations used in the management of certain diarrheal conditions and disturbances of the intestinal microbiota

4 MARKETED PRODUCTS

B. SUBTILIS

Dosage form

Capsules, powder or granules

Clinical target:

Reduction of digestive symptoms such as indigestion and bloating
Modulation of the immune system and gut microbiota

B. CLAUSII

Dosage form

Oral suspensions (in ampoules) represent the most common form; additional forms consist of capsules and powders/granules.

Clinical target:

Targeted management of diarrhea

ENTEROGERMINA

Oral suspension

- ***B. clausii*** (chủng SIN, O/C, T, N/R) – 4 x 10^9 CFU
- Indications: intestinal microbiota disturbances, impaired absorption of endogenous vitamins, and support for restoration of the intestinal microbiota

MEDILAC DS

Enteric-coated capsules

- ***B. subtilis*** (chủng R0179) *và* ***E. faecium*** (chủng R0026) – 1 x 10^9 CFU
- Indications: intestinal microbiota disturbances, loose stools, constipation, intestinal putrefaction, and flatulence

PROGERMILA

Oral suspension

- ***B. clausii*** (chủng UBBC-07) – 10 x 10^9 CFU
- Indications: during or after antibiotic therapy, support for maintaining intestinal microbiota balance, and daily immune support

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