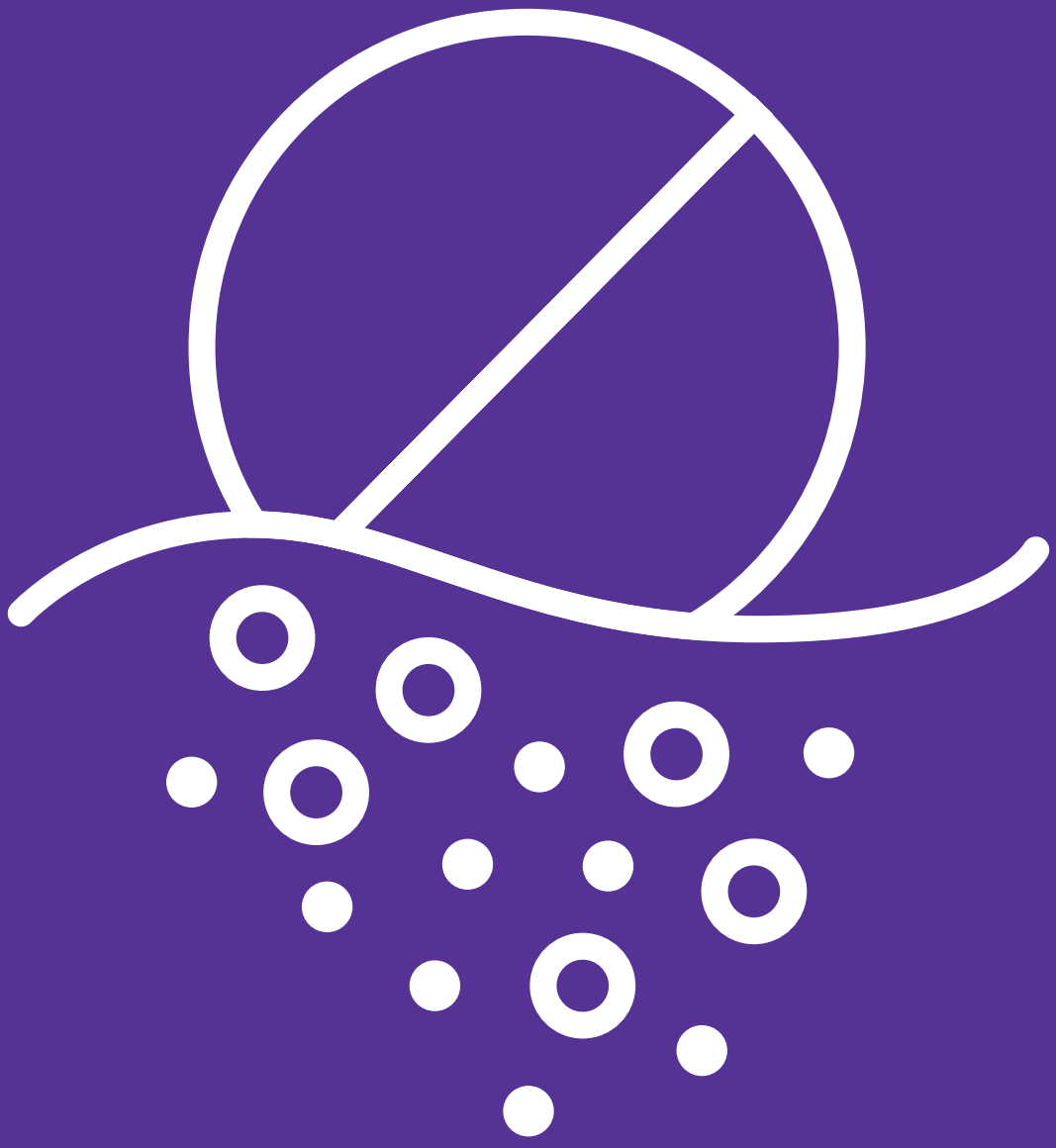
Nutrition & Biosciences

DUPONT™

Pharma Solutions

Alubra®

Our lubricant brings more to the tablet



Alubra® sodium stearyl fumarate delivers

Lubricants are a vital part of the tablet and capsule manufacturing process. Formulators have typically selected magnesium stearate to meet their needs as a familiar, well-established lubricant for oral solid dosage forms.

Magnesium stearate's hydrophobic structure provides excellent lubrication but it may also affect other product properties. Previous studies demonstrate that magnesium stearate can negatively impact disintegration and dissolution[1]. Blend times must be limited to avoid over-lubrication.

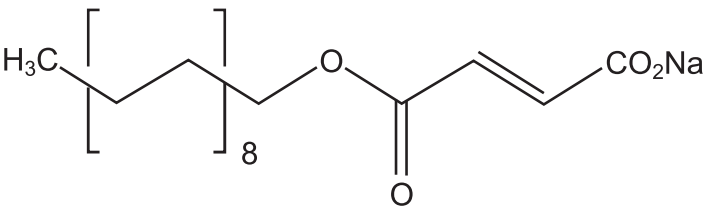
Formulators should consider these factors before selecting the appropriate lubricant for their formulation. Poorly soluble drugs, orally disintegrating tablets (ODTs)[2], and effervescent dosage forms will typically require a more hydrophilic lubricant.

Alubra® sodium stearyl fumarate offers many advantages compared to magnesium stearate. Our lubricant brings more to the tablet.

The chemistry of Alubra® provides important advantages

Alubra® sodium stearyl fumarate is less hydrophobic than magnesium stearate due to the presence of a fumarate group on the end of the structure. In addition to offering improved water dispersibility, the fumarate moiety of Alubra® increases the melting temperature, which allows greater functionality at high press speeds. The stearate chain of Alubra® maintains the lubricity of the compound, supporting low ejection forces and preventing sticking.

Chemical Structure of Alubra® Sodium Stearyl Fumarate



Product Benefits
Compared with the widely used lubricant magnesium stearate, Alubra® offers
Enhanced disintegration and dissolution
Improved compactability
Less sensitivity to blending time
Similar lubrication performance
Compatibility with a range of APIs

Typical Alubra® Properties	
Molecular Formula:	$C_{22}H_{39}NaO_4$
Formula Weight:	390.53
Melting Point:	220-240° C
Recommended Use level:	0.5-2.0% of Formulation
Chemical name:	2-Butenedioic acidiconoctadecyl ester, sodium salt
Acidity:	pH 8.3 (5% water solution at 90° C)
Solubility:	acetone practically insoluble ethanol practically insoluble methanol slightly soluble Water 1:5 90° C Water 1:20,000 25° C
BET surface area	2.0 – 4.0 m^2/g
Density (bulk)	0.2 to 0.3 g/cm^3
Density (tapped)	0.3 to 0.4 g/cm^3
EINECS #	223-781-1
CID #	23665634
CAS No.	4070-80-8

1. Chowhan, Z.T. and Chi, L.H. (1986); Drug Excipient Interactions Resulting from Powder Mixing IV: Role of Lubricants and their Effect on In Vitro Dissolution; Journal of Pharmaceutical Sciences, 75: 542-545. doi: 10.1002/jps.2600750604

2. Gebert, K. Meyer-Bohm, A. Maschke and K. Kolter; Compression Characterization and Lubricant Sensitivity of Orally Disintegrating Tablets Based on Lubiflash; Pharmaceutical Technology Europe, January 1, 2009, Volume 21, Issue 1

The surface area of Alubra® is tightly controlled

Product morphology (specifically surface area) has a significant impact on lubricant performance. Since the lubricating properties of SSF are dependent on its ability to coat other particles in a formulation during mixing, variations in surface area will impact the effectiveness of the coating and the amount of lubrication provided.

Specific surface area can be measured several different ways including laser scattering particle size distribution analysis. However, this method does not account for surface texture and assumptions are made regarding particle morphology.

A more accurate and widely used technique is the BET method. With BET, specific surface area is measured through the adsorption of gas molecules (i.e. nitrogen) onto a solid surface.

DuPont BioPolymer uses the BET method to measure the specific surface area of Alubra® since it is a widely accepted and reproducible method. Alubra® PG-100 has an internal surface area specification range of 2.0 – 4.0 m2/g using the BET method.

Alubra® meets the highest quality standards

Alubra® is manufactured under IPEC and cGMP conditions, which comply with recognized global quality standards. DuPont's own quality initiatives assure that the finished product is chemically, physically, and functionally consistent, as well as compliant with the stringent requirements of all major pharmacopoeias. DuPont carries out systematic product evaluation to ensure that Alubra® continues to meet or surpass these high standards.

SEM of Alubra® Sodium Stearyl Fumarate.

Alubra® Commercial Information

Alubra® complies with all major pharmacopoeias:

· NF	· Ph. Eur.	· CP
· JPE	· BP	

Commercial packaging:

- 1 KG drum
- 5 KG drum
- 25 KG fiber drum

Available supporting documentation for Alubra®:

- Specification Sheet
- MSDS
- COAs
- BSE/TSE Statement
- GMO Statement (Generally Modified Organism)
- Residual Solvent Statement (as per USP Chapter 467)
- Not of Human/Animal Origin Statement
- Allergen-Free Statement

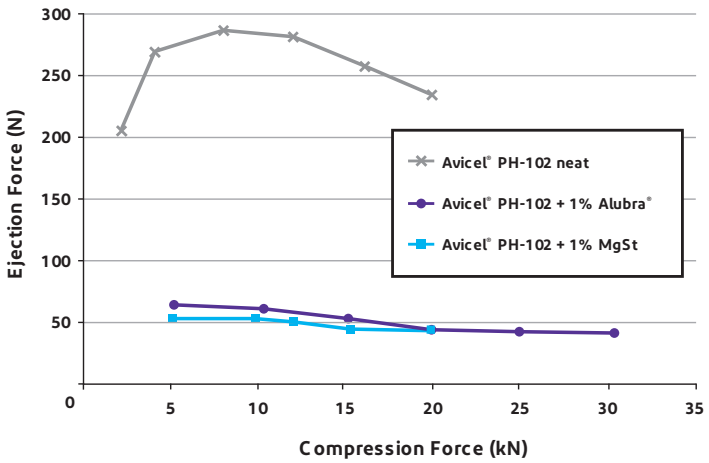
Alubra® offers the lubrication performance you need

During the tableting process, an extensive amount of friction is generated between the tablet and the surfaces of the die and punch as the tablet is ejected. This can impart considerable amounts of strain and shear on a tablet, resulting in defects such as sticking, capping, and lamination. Lubricants decrease ejection force, prevent sticking, and reduce overall manufacturing costs by preventing wear and tear on the tablet press.

The chemistry of Alubra® is unique in promoting improved wettability of the tablet, while still providing excellent lubricity even at higher tableting speeds. Alubra® has a higher melting point than magnesium stearate which allows for prolonged compression times at elevated compression forces.

Alubra® delivers lubrication comparable to magnesium stearate and allows for higher compression forces and faster press speeds.

Comparative Ejection Forces

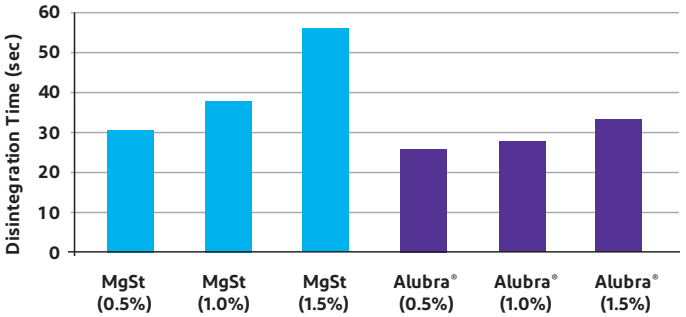


Alubra® improves the properties of effervescent tablets

Lubrication of effervescent tablets presents formulators with a challenge. Insoluble lubricants like magnesium stearate can negatively affect disintegration and solution clarity while water-soluble lubricants may not be as effective and may require high usage levels.

Alubra® provides excellent lubrication along with improved tablet hardness and disintegration time. After disintegration, magnesium stearate will also form a more visible surface film layer compared to Alubra®.

Comparative Disintegration Times of Vitamin C Effervescent Tablets



FORMULA

Ingredient	% Formula
Vitamin C	19.2%
Mannitol	30.3 - 31.3%
Anhydrous citric acid	18.7%
Sodium bicarbonate	30%
Aspartame	0.3%
Alubra® or Magnesium Stearate	0.5 - 1.5%

PROCEDURE

- Blend all ingredients except for lubricant for 2 minutes
- Add lubricant and blend for an additional minute
- ZP8 tablet press fitted with 20mm flat punch
- Tablet hardness: ~50 N
- Tablet weight: 2600 mg

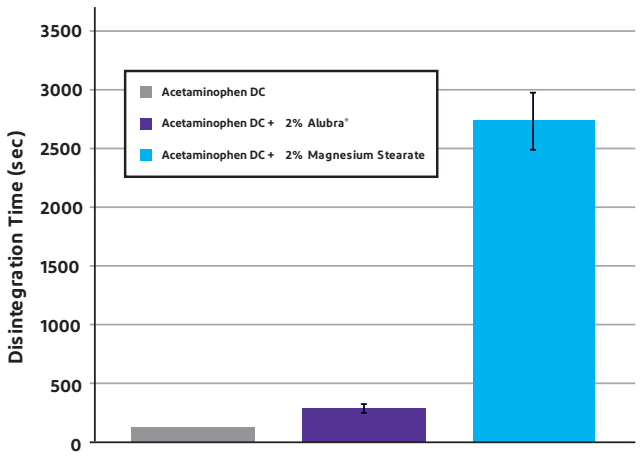
Alubra® offers improved disintegration

In the case of oral solid dosage forms dissolution is dependent, in part, on the disintegration of the tablet or capsule. Disintegration increases the surface area of the drug formulation which increases dissolution rate. Disintegration time will increase if a hydrophobic lubricant like magnesium stearate forms a film around drug/ excipient particles.

To illustrate this point, consider a directly compressible acetaminophen grade that contains starch and stearic acid. By using a high level of lubricant (2%) and blending for 5 minutes, a sufficient amount of coating or film is formed around the API.

If the lubricant is a hydrophobic material like magnesium stearate then disintegration will be considerably slower compared to an unlubricated control. Since Alubra® is less hydrophobic, it will have significantly less impact on disintegration time.

Comparative Disintegration Times of 500mg Acetaminophen Tablets



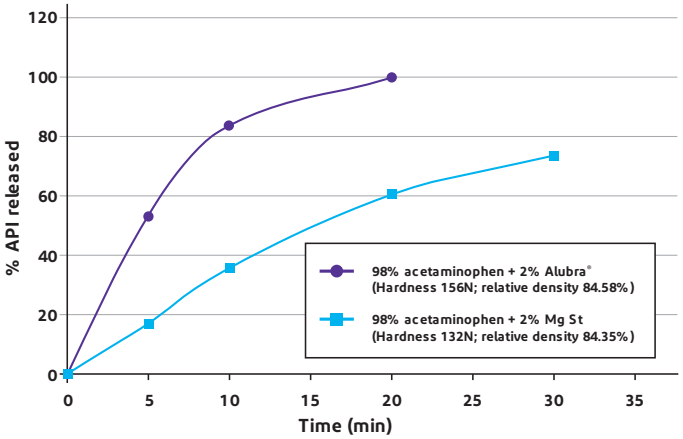
Alubra® enhances API dissolution

For an API to have acceptable bioavailability, it must dissolve in a reasonable period of time. This is a significant issue for drugs with poor or medium solubility. Hydrophobic lubricants like magnesium stearate exacerbate the problem since dissolution is further delayed[3].

Alubra® sodium stearyl fumarate is more hydrophilic than magnesium stearate so it interferes less with disintegration and dissolution.

In the same APAP model described above, the formulation with Alubra® results in significantly faster dissolution compared to the analogous formulation using magnesium stearate.

Comparative Disintegration Times of 500mg Acetaminophen Tablets



3. G.K. Bolhuis, C.F. Lerk, H.T. Zijlstra and A.H. de Boer; Pharm. Weekblad 110 317 (1975)

Alubra® is compatible with a wide range of APIs

Magnesium stearate has compatibility issues with several types of APIs, as shown in the table to the right[4]. For example, it is well known that some widely used APIs, like aspirin, are not compatible with magnesium salts.

Alubra® has few known compatibility issues and can be used with a variety of APIs.

Magnesium stearate is known to have compatibility issues with several types of APIs

Antiviral
Acyclovir

Anti-inflammatory
Aspirin
Ibuproxam
Indomethacin
Ketoprofen

Antidiabetic
Glipizide
Chlorpropamide
Glimepiride
Glibenclamide

Antihypertensive
Captopril
Fosinopril
Moexipril
Oxprenolol
Quinapril

Antibiotic
Cephalexin
Erythromycin
Nalidixic Acid
Oxacillin
Penicillin G

Antimalarial
Primaquine

Antiemetic
Promethazine

Antiamoebic
Albendazole

Anticancer
ß-lapachone

Anticoagulant
Clopidogrel

Antihistaminic
Doxylamine

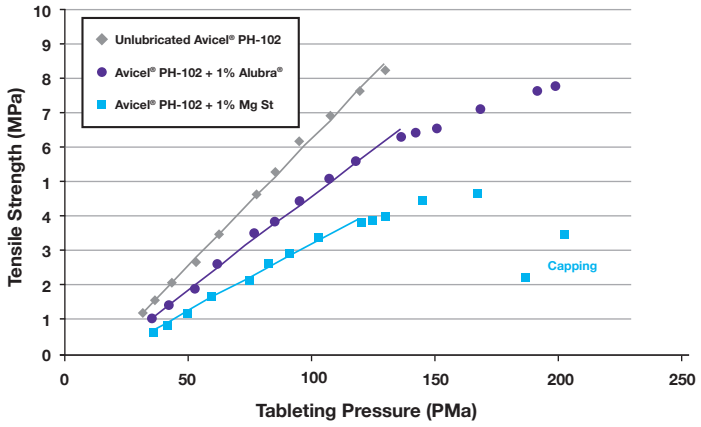
Hypnotic
Temazepam

Alubra® provides better tablet hardness and allows for high compression forces

A tablet hardness analysis with microcrystalline cellulose indicates that Alubra® offers superior compression versus magnesium stearate across the complete compression profile.

When compactability was measured on a tablet press, the formula using Alubra® resulted in the hardest tablets, indicating that Alubra® is a better choice than magnesium stearate when it comes to high-speed tableting, and/or higher compression forces.

Comparative Tablet Strength



FORMULA

Ingredient	% Formula
Avicel® PH-102:	99
Alubra® or Magnesium Stearate:	1

PROCEDURE

- Materials: Avicel® PH-102 + 1% lubricant (Alubra® or MgSt) and Avicel® PH-102 neat
- Sieved through 710µm
- Blending time 5 minutes
- ESH Compaction Simulator
- 13-mm round, flat faced punches
- Tablet weight: 500 mg
- Cycle time: 0.12 seconds
- Dwell time: ~6 milliseconds

4. Sonali S. Bharate, Sandip B. Bharate, and Amrita N. Bajaj; Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review; J. Excipients and Food Chem. 1(3) 2010; November 2010

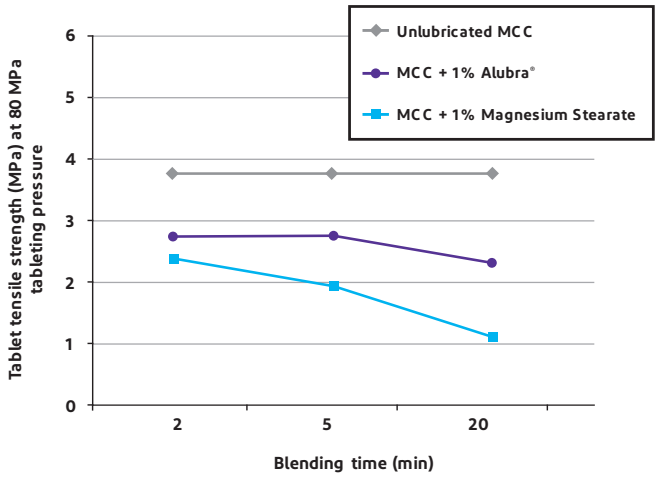
Alubra® is less sensitive to increases in blend time

Lubricants generally decrease tablet strength, however this impact is relatively small given the low usage rate. The exception is when mix times are increased and the blend becomes over-lubricated. This will cause most lubricants, including magnesium stearate, to significantly weaken tablet strength.

The graph to the right shows microcrystalline cellulose tablet tensile strength vs. blend time for magnesium stearate and Alubra®. Increasing blend time from 2 minutes to 5 minutes has no effect on Alubra® but the magnesium stearate tablets lose tensile strength.

At 20 minutes, Alubra® tablets will lose some strength but the hardness is still acceptable. Magnesium stearate will significantly limit the compressibility of MCC with this blend time, possibly leading to tablet defects. Unlike magnesium stearate, Alubra® does not require a separate blend step to minimize mixing time.

Comparative Tablet Strength as a Function of Blend Time



Alubra® increases manufacturing flexibility

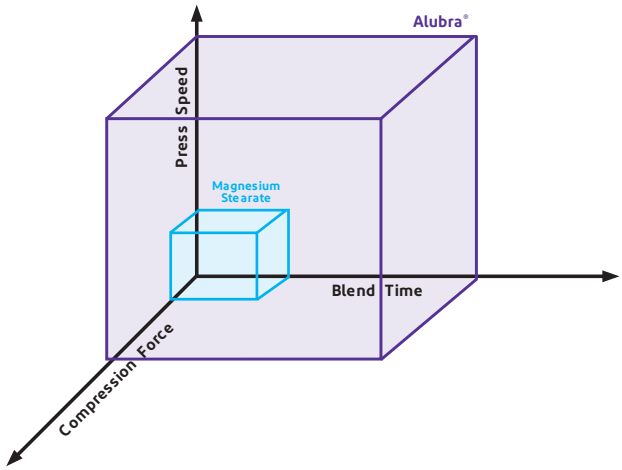
Magnesium stearate imposes several limitations on the manufacturing process of oral solid dosage forms.

Blend times must be kept to a minimum since over-blendingcan negatively impact dissolution and compactibility. Alubra® is much less sensitive to blend time so it can be added earlier in the process, eliminating an additional blend step for the lubricant. Alubra® can also be used to provide lubrication during the roller compaction process.

Magnesium stearate will cause tablets to become less compactable at higher compression forces. Alubra® provides excellent tablet hardness across the complete compression profile. Also, sodium stearyl fumarate has a higher melting point that magnesium stearate (220 – 240oC vs. 120 – 150oC) which allows for faster tablet press speeds and higher throughput.

Alubra® increases the manufacturing “sweet spot” allowing for more flexibility and simplifying production site transfers.

Comparative Operating Window for Manufacturing



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