



STICKING &  
PICKING  
SCALE-UP  
CHALLENGES  
MOLECULAR  
CHARACTERIZATION  
**PROTOTYPE**  
FORMULATION  
PRE-FORMULATION  
MOLECULAR  
CHARACTERIZATION  
**SCALE-UP**  
CHALLENGES  
PROTOTYPE  
FORMULATION  
STICKING & PICKING  
PRE-FORMULATION  
PROTOTYPE FORMULATION  
SCALE-UP CHALLENGES



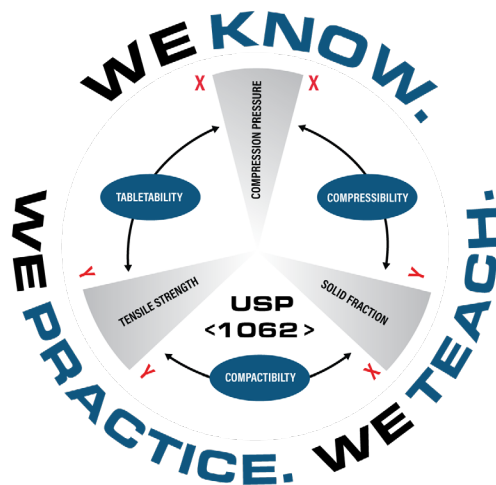
**NATOLI**  
**SCIENTIFIC**  
a division of Natoli Engineering Company, Inc.

[natoliscientific.com](http://natoliscientific.com)

## PARTNER WITH NATOLI

Use our expertise in material chemistry and powder mechanics to address tableting issues during the earliest stage.

**Save cost and time in development!**



# NATOLI SCIENTIFIC

WILL HELP YOU DEVELOP YOUR TABLETS  
FROM MOLECULES TO MARKET

## TROUBLE-SHOOTING CHALLENGING MOLECULES



**Material  
Chemistry**

+

**Powder  
Mechanics**



Natoli Scientific Discovers the  
**ROOT CAUSE** of Any Problems and Provides  
Scientifically Based Sound Solutions

*and*

Partners with You to Develop a  
Scientifically-Sound Robust Formulation



**OUR PREFORMULATION STUDIES AVOID  
LATE-STAGE DEVELOPMENT SURPRISES...  
SAVING COST AND TIME!**



# CUSTOMIZED SOLUTIONS TO MEET YOUR TABLETING CHALLENGES



## PREFORMULATION SERVICES

Formulation analysis services including:

- API characterization
- Stability testing
- Method validation protocols
- Dissolution testing

## FORMULATION DEVELOPMENT

Formulation development, modification, and testing services including:

- Development strategies
- Scalability solutions
- Compaction simulation

## PRODUCTION/ MANUFACTURING

Small batch non-GMP CDMO support/services

## TECHNICAL TRAINING

Regularly scheduled and customized technical training courses provide:

- Classroom and hands-on learning
- On-site and off-site availability

## HEADQUARTERS' SERVICES:

Home to the Largest Automated Premium Tooling Manufacturing

## TOOLING RECOMMENDATIONS

Tool steel and material selection to optimize tableting efficiency. In house PVD coating services to mitigate sticking and picking issues, to enhance tooling life-span

**TabCad** — FREE web-based computerized tablet design with free consultative service from our expert tablet designer

## DATA ACQUISITION SYSTEMS

Natoli AIM™ Instrumentation and software upgrades  
NP-RD10A Single-station tablet press  
NP-RD30 Rotary development & scale-up tablet press

## TABLET PRESS & CALIBRATION SERVICES

Meet regulatory compliance with tablet press calibration services:

- Instrumented tablet presses & calibration
- Preventive maintenance services
- Tablet press assessment

# DEVELOP WITH A PURPOSE

Natoli Scientific helps you avoid or solve issues that may arise during tablet compression, whether you're in the initial stages of research and development or troubleshooting an existing formulation.

We take a proactive approach to formulation development. Natoli Scientific actively looks for possible indicators during development that may impact scale-up and commercial production.

By identifying issues earlier in the process, we can recommend solutions to help you avoid time-consuming troubleshooting and reduce long-term costs. Natoli Scientific's team of experts will work with you to find the options and solutions that will best serve your objectives.

## Preformulation/Analytical Capabilities

### Basic Compression Studies [USP<1062>]:

- Natoli RD 10a / AIM Data Acquisition System

### Advanced Compression Studies:

- Presster compaction emulator
  - » API and excipient characterization
    - Characterize new materials
    - Compare batch-to-batch variability
    - Guidance on excipient vendor changing/selection
  - » Manufacturing predictions
    - Formulation scale-up assessment
    - Press simulations
    - Tooling trials
  - » Compression science
    - High speed dynamic compaction data
    - Heckel analysis
    - Work descriptors of compactions process
    - Shapirao's equation
    - Immediate axial recovery
    - Ejection forces
    - Strain rate sensitivity (Scale-up risk indicator)
    - USP<1062> [Compressibility, Compactibility, Tableability]
  - » Formulation trouble shooting
    - Picking
    - Sticking
    - Capping
    - Lamination



*Single-station R&D press with data acquisition and analytical software.*



**The Presster** can test a single tablet at production speed from a library of press models including **Fette, Korsch, Romaco, Syntegon**.

#### Density Measurements:

- Bulk and tapped density measurement
- Helium pycnometer

#### Granule Characterization:

- Particle size measurement (Sieve analysis:  $d_{10}$ ,  $d_{50}$ ,  $d_{90}$ )
- Moisture analyzer (Loss on drying)

#### Powder Flow Measurements:

- FT4 powder rheometer
  - » Assessment of punch sticking
  - » Complex powder flow behavior characterization
    - Cohesion index
    - Internal angle of friction
    - Angle of repose

#### USP Recommended Tablet Testing:

- Tablet breaking force (hardness) tester
- Tablet friability testing
- Tablet disintegration testing
- Tablet dissolution testing

#### Stability Studies:

- ICH stability chambers (Humidity and Temperature controlled)
- pH meter
- Agilent HPLC

## Additional Analytical Capabilities

- Powder X-ray Diffractometer
- Q2000 high sensitivity DSC thermal analysis instrument
- Q5000 high sensitivity TGA thermal analysis instrument
- Q5000 SA dynamic moisture sorption analyzer
- Malvern Mastersizer 3000 with dry powder feeder particle sizer ( $d_{10}$ ,  $d_{50}$ ,  $d_{90}$ )
- Karl Fisher titration (Water content)
- PerkinElmer® ATR-FTIR
- Zetasizer Nano ZS
- Shimadzu UV-1240 UV spectrophotometer

## Formulation Development Capabilities

#### Blending:

- V-blender (2-quart, 4-quart, 1 cu.ft., 5 cu.ft.)

#### Wet Granulation:

- High shear granulator (Manufacturer: Diosna, Model: P 1-6)
- Low shear granulator
- Fluid bed granulator (Manufacturer: Diosna, Model: Minilab RC)

#### Dry Granulation:

- Roller compactor (Freund-Vector)

#### Milling: (Manufacturer: Frewitt)

- Oscillation mill (Model: Oscillowitt-Lab)
- Hammer mill (Model: Hammerwitt-Lab)
- Co-mill (Model: Coniwitt-Lab)

#### Tablet Manufacturing:

- Natoli NP-RD 30 (4B & 4D station) with AIM Data Acquisition System

#### Tablet Coating:

- Tablet coater (Manufacturer: Diosna, Model: Minilab RC)
- Fluid bed coater (Manufacturer: Diosna, Model: Minilab RC)

## Production-Scale Capabilities

#### Blending:

- V-blender (20 ft<sup>3</sup>)

#### Dry Granulation:

- Roller compactor (Freund-Vector)

#### Tableting:

- Natoli NP-400 (22 stations)

# FORMULATION DEVELOPMENT & MODIFICATION

Developing a robust tablet formulation that is successfully scaled up to product manufacturing can be challenging. In fact, many manufacturing issues can be traced back to the formulation. At Natoli Scientific, we have developed a rigorous and creative stepwise approach to pro-actively identify mechanical deformation properties and issues with an API that affect processability.

As a critical first step, Natoli Scientific evaluates the characteristics of your formulation to determine which product and mechanical modifications will enhance tabletability. Our experts test the proposed modifications and suggest actions, such as blending or granulation to further improve tabletability of your

product. We'll help you identify the correct excipients to use based on your API's behavior. Natoli Scientific will also test product flow and particle size distribution to determine whether dry or wet granulation is required.

## Our testing provides:

- Tabletability and compactibility profiles
- Compaction simulation data (e.g. Heckel plots, work curves)
- Ejection profiles to optimize powdered lubrication

*...and more!*

## Let us assist you in your challenges with:

### PRE-FORMULATION AND FORMULATION DEVELOPMENT

- » Material characterization
- » Formulation design
- » Release profiles – immediate, extended, etc.
- » Powder flow

### GRANULATION

- » Particle size
- » Friability
- » Sticking
- » Processability
- » Agglomeration

### MILLING

- » Particle size distribution
- » Blade and screen type selection
- » Extrusion

### HOT MELT EXTRUSION

- » Polymer selection
- » Crystallinity (vs. amorphous)

### TABLET DESIGN OPTIMIZATION

- » Sticking/picking
- » Capping/lamination
- » Discoloration
- » Scalability

### COATING

- » Twinning
- » Spray drying
- » Orange peeling
- » Color uniformity

### BLENDING

- » Order of addition
- » Lubrication times
- » Uniformity studies





# SCALE-UP SUPPORT

The transition from development to full-scale production can lead to unwanted surprises. Natoli Scientific's laboratory capabilities provide detailed powder characterization studies and scale-up assistance using limited quantities of material. Our Telford, Pennsylvania laboratory features a fully instrumented **Presster Compaction Emulator** that can test single tablets using less than one gram of API.

Our experts will determine how your formulation will perform during full-scale production by running tests on the **Natoli NP-RD30** rotary tablet press. This innovative press will match the dwell times, turret speed, and vertical punch velocities of your production press.

## Our scale-up support provides:

- Formulation modification to improve tablet quality
- Tabletability and compactibility profiles
- Measurements for compression cycles: dwell time, turret velocity, vertical punch velocity, etc.
- Containment/Clean-up protocol creation
- Your formulation's character material deformation properties
- A library of data that allows simulation of production speeds for most brands of tablet press
- On-site consulting services



**Natoli's NP-RD30** replicates the design and functionality of a full-scale production press.



## TABLET DESIGN RECOMMENDATIONS

Natoli Scientific experts can recommend an efficient and effective tablet design for your product based on your formulation's characteristics and your manufacturing requirements and restrictions.

## TOOL MATERIAL & COATING RECOMMENDATIONS

The proper tool steel type, tool coating, and die configurations are critical to successful tableting, particularly for difficult formulations. Natoli Scientific will recommend tooling materials to support your product and keep production running smoothly.

# R&D ANALYTICAL AND PRODUCTION CONTROL SOFTWARE

## FOR R&D TABLET PRESSES

Natoli Scientific can retrofit your current R&D press with **Natoli AIM™ Data Acquisition and Analytical Software** to enhance and simplify your R&D processes. Our industry-leading software combines tableting data imported from your press and manually entered tablet parameters to automatically

generate plots for tableability, compactibility, compressibility profiles, and more that goes straight into Microsoft Excel.

If your current press already has analytical software, our experts can customize an upgrade to include the advanced features and benefits of **Natoli AIM™ Data Acquisition and Analytical Software**.

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## FOR PRODUCTION TABLET PRESSES

Enhance the performance of an outdated production press with the **Natoli AIM™ ProPlus Custom** control system. Tailored to your specific requirements, **Natoli AIM™ ProPlus Custom** control systems are designed to:

- » Improve ease of operation of your existing tablet press
- » Increase tablet production
- » Report 21 CFR Part 11-compliant data
- » Reduce product loss
- » Improve tablet quality
- » Reduce tableting costs

The **Natoli AIM™ ProPlus Custom** control system is network-ready with secure datasets that meet the **FDA's** electronic records requirements. Report generation and storage are easy, and batch reports can be transferred to secure network drives for shared views, data backup, and secure storage. Press operators can easily and quickly generate:

- » Activity/performance reports
- » Product and variation reports (RSD)
- » Batch and end-of-batch reports
- » Error code and alarm reports
- » Audit trail of changes during batch production



*Reconditioned Kikusui press with enhanced control system.*



# HANDS-ON TECHNICAL TRAINING

Natoli Scientific's regularly scheduled and customized training courses provide comprehensive insight into tablet development, scale-up, manufacturing, and more within a unique classroom setting and through hands-on experiences. Our technical training incorporates expert panel discussions, problem-solving exercises, live demonstrations, one-on-one consultations, open peer discussions, and Q&A.

Training instructors include Natoli technical experts, and other industry thought leaders who share their knowledge directly with you. Attendees can present their challenges not only to the instructors but also to their peers who may have encountered similar problems and developed unique solutions.

Our training courses enable you to see the real-world applications of the lectures and participate in hands-on laboratory exercises.



## LEARN

new approaches to  
formulation  
development

## BUILD

relationships for  
lasting support with  
industry experts  
and peers

## ENHANCE

critical thinking and  
problem-solving skills

## APPLY

scientific principles to  
your own formulation  
development

# KNOWLEDGE & EXPERIENCE SHARING

## WHO SHOULD ATTEND?

Our training events are designed for those involved in tableting R&D including:

- » Compounding pharmacists
- » Formulation scientists
- » Research associates
- » Technology transfer scientists
- » Process and validation engineers
- » R&D Directors
- » Technical Project and Product Managers
- » Manufacturing Supervisors



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## LEARNING OBJECTIVES

Attendees will obtain a greater understanding of the following topics:

- » Formulation development strategies
- » Excipient selection
- » Blending
- » Powder rheology
- » Compaction emulation
- » Tablet design
- » Granulation (roller compression, high shear, fluid bed)
- » Tablet compression with scale-up
- » Tablet coating

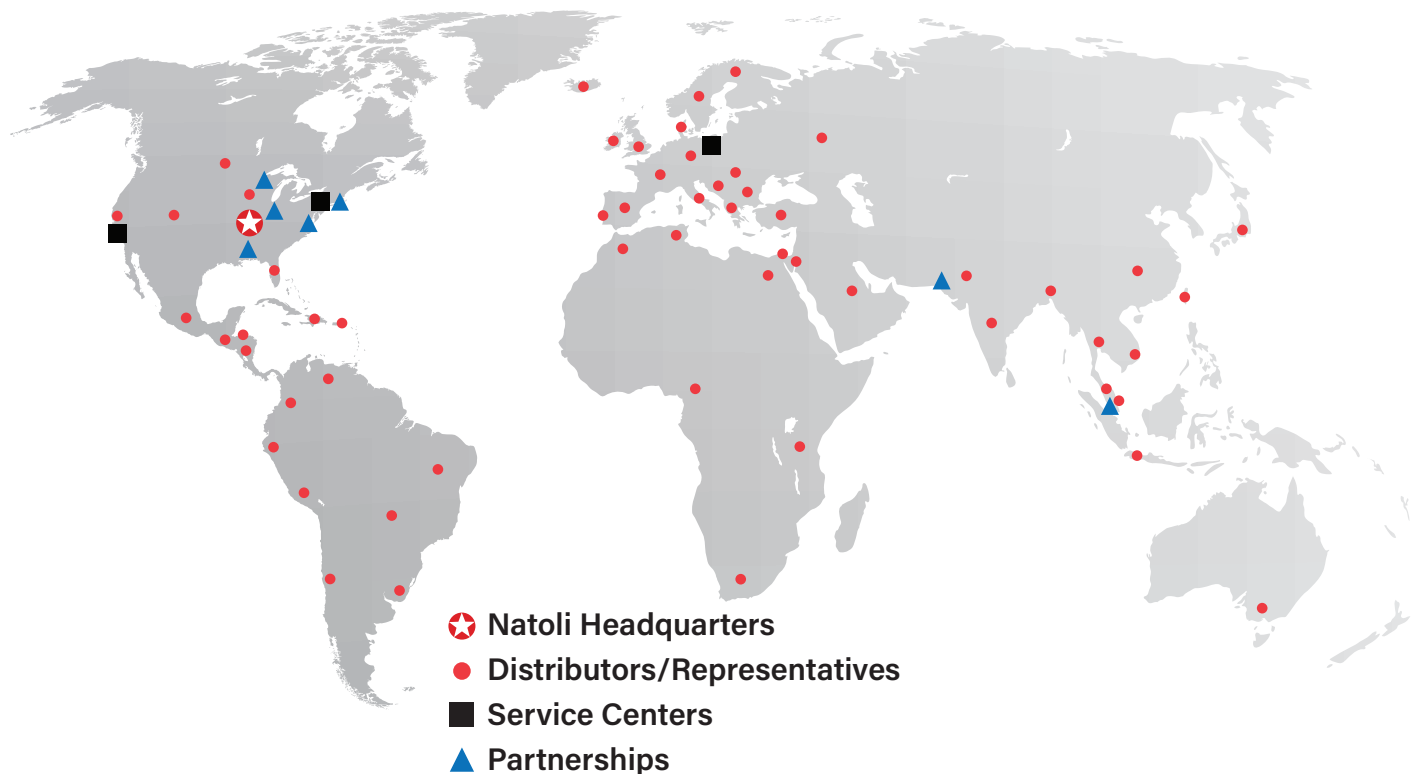


Check **[Natoli.com/trainings](http://Natoli.com/trainings)** for upcoming training dates or customized on-site training availability!



# WORLDWIDE SUPPORT

## Benefits Customers & Industry



*With laboratory facilities in Missouri and Pennsylvania, and support from our partnerships, regional representatives, and service centers, Natoli Scientific has resources available to assist you worldwide.*

## INVESTING IN EDUCATION

### for the future of development in pharmaceutical manufacturing

Natoli Engineering supports education and values its partnerships with universities as they propel advancements in tablet compression and continuous manufacturing. Natoli's support gives students hands-on experience while they work to establish industry best practices and prepare for their careers.

Natoli is an active member of C-SOPS (Center for Structured Organic Particulate Systems), which allows industry leaders and universities to work together to improve the pharmaceutical manufacturing process. By collaborating with the next generation of tablet compression experts, Natoli can continue to drive innovations in tableting.







[natoliscientific.com](http://natoliscientific.com)



### **Natoli Scientific R&D Laboratory**

**100 Emlen Way, Suite 104-108, Telford, PA 18969**

Our state-of-the-art R&D laboratory in Telford, Pennsylvania houses a full range of bench-top R&D and production tablet presses, dry and wet granulation machines, a compaction emulator, and coating equipment. The troubleshooting and custom research services we perform address each stage of product development.



### **Natoli Headquarters**

**28 Research Park Circle, Saint Charles, MO 63304**

Natoli Engineering Company is the world-renowned leader in tablet press tooling manufacturing. But we are far more. Founded on the uncompromising principle to manufacture and deliver the highest quality products at a fair price with exceptional customer service, Natoli continues to build on 50 years of innovation and industry leadership.



### **Natoli Technical Training Center**

**St. Charles, MO**

The St. Charles facility offers classroom and hands-on tablet manufacturing process training. Natoli Scientific classes help those involved with R&D learn about granulation principles and best practices; common excipients and their designed functions; factors that can influence successful tablet coating; and the importance of characterization, measurement, blending, and more.



**NATOLI INSTITUTE**  
LONG ISLAND UNIVERSITY



**NATOLI-BCP RESEARCH & TRAINING LAB**  
THE BOMBAY  
COLLEGE OF PHARMACY