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Mixing

**IN A
COMPOUNDING
PHARMACY
IN THE 21ST
CENTURY**

ABSTRACT

When it comes to combining ingredients for topical preparations, compounding pharmacists utilize either the manual methods such as a spatula and pill tile or a mortar and pestle, typically an electronic mortar and pestle. If a topical preparation must be pre-ground or requires trituration, or any level of particle-size reduction, historically the manual method of combining ingredients in such a preparation would include the initial use of a mortar and pestle; however with micronized substances this is not as much a concern today as in the past. There is, of course, the concern of a lack of reproducibility, knowing that each compounder might utilize the equipment differently, would mix for varying times, and would also mix with varying amounts of physical pressure applied to the pestle. If the discipline of uniform usage is great enough in the lab, this method could probably produce consistent results, but, because of the preparation and cleanup time and the fact that newer technology is available, this method is not recommended as the common compounding method in a compounding pharmacy that does more than a handful of compounded topical preparations per week. This article is not meant to say these methods are not appropriate, but, rather, to point out that newer technology is available and might be preferable in order to provide a cleaner, more efficient, and more reproducible lab environment.



Rob Standridge is affiliated with three pharmacies as President: Blanchard Drug & Gift, LegendCare Pharmacy, and Hominy Drug & Gift, President and founder of RS Software, President of Health Engineering Systems, Inc., and currently serving as Senator for central Oklahoma and Chairman of Health in the Oklahoma State Senate.

Today's compounding pharmacist is asked to provide more and more expertise in the world of customized medications; therefore, pharmacists should be equipped with technology that makes their jobs as efficient, simple, and reproducible as possible.

When it comes to combining ingredients for topical preparations, compounding pharmacists rarely utilize the manual methods from the 20th Century such as a spatula and pill tile or a mortar and pestle. Rather, modern pharmacists take advantage of the electronic mortar and pestle (EMP).

By utilizing the closed mixing system offered by an EMP, a pharmacist saves significant time, is able to provide a much more hygienic preparation and dispenser, and is able to reproduce the same results each and every time they compound.

Fortunately for compounding pharmacists, the Unguator technology has been around since the mid-1990s. However, little change has been made to improve the technology over that time. Thanks to Gako, a German Engineering Company, and Albrecht Konietzko, its founder, a pharmacist and the inventor of the Unguator or EMP, and the hard work of their designers and engineers over the last few years, in 2016, we will see innovative changes and advancements in the soon-to-be-released new Unguators or EMPs that we have not seen since their initial release.

HOW DO WE MIX TODAY?

WITHOUT AN ELECTRONIC MORTAR AND PESTLE

In the past, a compounding pharmacist or their technician would decide whether a topical preparation should be mixed only or if the preparation should be ground or triturated before mixing. If mixed only, the ingredients could be combined on a glass pill tile utilizing two spatulas sized according to preference. Although this method if performed diligently and thoroughly enough can result in a homogeneous, elegant mixture, if not done properly the compounder could end up with a non-uniform mix, but a mix that might look uniform. This mixing method would not be recommended if uniform concentration is critical to the safety of the patient, and in today's compounding world where reproducibility is not just desired but demanded, this method falls short if the compounder is not completely confident of its thorough application each and every time. Add to this the fact that this method is somewhat messy and requires significant setup and cleanup, and we realize that another method might be preferable.

If a topical preparation must be pre-ground or requires trituration, or any level of particle-size reduction, historically the manual method of combining ingredients in such a preparation would include the initial use of a mortar and pestle. Studies have shown that a mortar and pestle when used correctly does a good job of reducing particle size and producing a homogeneous preparation. If this method is preferred by a compounding pharmacist, they would likely have several sizes of mortars and pestles to accommodate various volumes of preparations. Certainly, again, we have the concern of a



lack of reproducibility, knowing that each compounder might utilize the equipment differently, would mix for varying times, and would also mix with varying amounts of physical pressure applied to the pestle. If the discipline of uniform usage is great enough in the lab, this method could probably produce consistent results, but, because of the preparation and cleanup time and the fact that newer technology is available, this method is not recommended as the common compounding method in a compounding pharmacy that does more than a handful of compounded topical preparations per week.

These are the two manual methods typically employed currently and in the past in the compounding of topical preparations. This article is not meant to say these methods are not appropriate, but, rather, to point out that newer technology is available and might be preferable in order to provide a cleaner, more efficient, and more reproducible lab environment.

Although the Unguator is the only EMP and closed mixing system with the capability of some particle-size reduction implemented in the North American market, there are other technologies that either provides some alternative methods of mixing or complementary preparation of a formulation when mixing is required. One such technology is the resonant acoustic mixer (RAM), which is being implemented in some pharmacy compounding practices to assist in mixing within a closed system. This technology is primarily being used in the fast mixing of powders for encapsulation, an operation that can also be implemented by the Unguator technology.

Often pharmacists and compounding technicians perceive the ointment mill as a competitive piece of equipment to the Unguator or EMP; however, the more accurate comparison is that the Unguator or EMP and the ointment mill are complementary technologies more effectively used in combination. A compounder must remember that when something is milled it does not necessarily mean that it is mixed, and to ensure a homogeneous preparation a formulation must be mixed after it has been milled. In fact, the most commonly recommended method to prepare a topical preparation if both an EMP and an Ointment Mill are being utilized is to mix-mill-mix.

HERE ARE SOME COMPOUNDING METHODS RECOMMENDED BY THE UNGUATOR OR EMP ENGINEERS IN SOME SPECIFIC SCENARIOS WITH THE USE OF AN UNGUATOR OR EMP. SUSPENSION OINTMENTS

Suspension ointments (or creams) are preparations in which one or more micronized solids are dispersed uniformly throughout a base but not dissolved.

SUSPENSION WITH AN ACTIVE SUBSTANCE CONTENT OF LESS THAN 2%

Unlike other mixing methods, the EMP can perform the mixing of a suspension ointment in the same container in which pharmacy dispenses the suspension.

First, weigh out 30% of the base directly in the EMP jar, being sure to spread the base where it fully covers the bottom of the jar and forms a seamless connection with the wall all around the jar. Next, weigh the active ingredients by placing on the top and near the edges of this base layer the active ingredients (could also include the other inert ingredients here as well). Next, cover this with a small amount of the base, leaving the majority of the base to mix in after the pre-grinding operation. This method of filling the EMP jar with the formula ingredients is referred to as the *sandwich* method.

It is important that a standard mixing blade (SMB) be used for a suspension, as the SMB provides the most physical action against the wall of the EMP jar, thus breaking up any lumps and providing a homogeneous pre-grinding process.

Now, run the pre-grind operation in the Unguator 2100 or Unguator Pro according to the program included for Suspension <2% or in the Unguator E/S or Unguator EMP according to the chart below. In the Unguator E/S, Unguator EMP, or Unguator B/R, you should pre-grind at 2000 to 2100



RPMs, which is turning the speed knob completely to the right for the B/R or on rotation setting 8 to 9 on the Unguator E/S or Unguator EMP.

Once the pre-grind operation is complete, you should inspect the formulation to make sure it is homogenous. The pre-grind operation can be repeated several times if needed. Once satisfied with the pre-grind results, you should add in the remaining base and any other ingredients according to the sandwich method and mix in the Unguator 2100 or Unguator Pro, according to the program already started, or in a Unguator E/S or Unguator EMP, according to the chart below.

Here are the pre-grinding and mixing times on the Unguator E/S or Unguator EMP for the mixing of a Suspension <2%:

	Jar size	15 mL to 30 mL	50 mL to 100 mL	200 mL to 300 mL	500 mL	1000 mL
1. Step	Pre-grinding	0:30	0:30	1:00	1:30	1:30
2. Step	Main Mix	1:30	2:00	3:30	4:40	6:45

Note: Units of time in chart above are expressed in Minutes:Seconds (MM:SS).

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SUSPENSION WITH AN ACTIVE SUBSTANCE CONTENT OF GREATER THAN 2%

Because of the higher concentration of solids in this suspension, a pre-grinding period is not needed. By use of the SMB and prolonged stirring, the solids are wetted thoroughly and a homogeneous mix results. Like previously, you should weigh out your ingredients for this preparation according to the sandwich method.

EMULSION OINTMENTS

Emulsion ointments are formulations where an aqueous phase and an oily phase are combined. The mixing method is the same for an emulsion whether the emulsion is a water-in-oil (W/O) emulsion, an oil-in-water (O/W) emulsion, or a quasi-emulsion. A solution ointment can also be treated like an emulsion ointment when preparing with an EMP.

STANDARD EMULSIONS

Like the suspension previously, you can weigh your ingredients out directly in an EMP jar, and you should use the sandwich method. The oily phase should be weighed out first and made to cover the bottom of the jar. Unlike the suspension, you can use a disposable blade for mixing emulsions. The disposable blade while mixing provides a greater frequency of contact with the ingredients of the formulation in contrast to the SMB.

EMULSION PLUS

These are emulsions that require heat treatment in order to melt one or more of the ingredients. First, you can melt the appropriate ingredients in a mixing bowl or directly in the EMP jar (Unguator EMP jars are heat stable up to 85°C/185°F) and mix by hand or in Unguator until cool. If the formulation contains water, it can be heated in a microwave (do not overheat). After this, the preparation is mixed on the EMP machine.

GELS

First weigh out the aqueous phase directly in the Unguator EMP jar and add the active ingredient to this. Add the gelling agent last. Mix by using a disposable blade and alternating mixing speeds between fast

FEATURES OF THE GAKO UNGUATOR BASIC, ELECTRONIC MORTAR AND PESTLE, AND PRO.

GAKO UNGUATOR BASIC & EMP - FOLLOWS IN THE TRADITION OF THE E/S AND E/R	GAKO UNGUATOR PRO - THE ULTIMATE TO MIXING IN A CLOSED SYSTEM
<ul style="list-style-type: none"> Preparation according to CGMP for semi-solid preparations up to 500 mL Quick-lock coupling Touch screen Intuitive user guidance Setting of mixing time Ten mixing speed settings Integrated time recording of total mixing time Identification number generated after each mixing process Integrated quality assurance validation (IQ/OQ) RS232 interface port Control, validated mixing programs and updates available through external Gako software Quiet operation due to optimized mechanical system and electronics More compact setup with enhanced performance Extensive accessories 	<ul style="list-style-type: none"> Preparation according to CGMP for semi-solid preparations up to 2000 mL* Mixing jar sizes up to 2000 mL* Preparation in a medicine bottle* Quick-lock coupling Interchangeable lifting arm 10.1-inch touch display Intuitive user guidance includes validated mixing programs Integrated barcode reader Integrated (optional) Gako software Automatic online updates free of charge Interface for laboratory balances, printer, peripheral equipment, network with 4 USB, 3 RS232, and 1 RJ45 Port/-s Integrated functional check (IQ/OQ) Remote inspection with Gako software available Integrated help/support menu Quiet operation due to optimized mechanical system and electronics More compact setup with enhanced performance Rinsable key pad and extensive accessories
BASIC vs. EMP at a Glance	
BASIC: Performance by hand with manual vertical lifting	- More compact setup with enhanced performance
EMP: Automatic lift guide	- Rinsable key pad and extensive accessories

*2000-mL availability anticipated by the end of 2016. CGMP = Current Good Manufacturing Practices; IQ = installation qualification; OQ = operational qualification

stirring and slow stirring to provide a smooth finished gel (50 mL in about 25 minutes).

Gel preparations should be stirred until the formulation is uniformly gelled and the mixture is homogeneous. To accelerate the gelling process, you can alternate between fast and slow mixing, alternating between 2000 to 2500 RPMs and 250 to 650 RPMs. This is automated in the program of an Unguator 2100 or Unguator Pro but handled by the compounder with an Unguator E/S or Unguator EMP.

Start with a higher speed to prevent agglomerations and to wet the gelling agent with the liquid phase. The stirring time depends on the size of the formulation.

Stirring times for gel preparations:

	Jar Size	RPM	15 to 100 mL	50 to 300 mL	200 to 500 mL	
1. Step	wet	2100	0:30	0:30	0:30	1:00
2. Step	swelling phase	650	08:30	9:30	9:55	9:55

WHAT IS IN STORE FOR COMPOUNDING PHARMACISTS WITH THE NEW UNGUATOR OR EMP TECHNOLOGY?

Today, compounding pharmacists and their technicians prefer to use an EMP when they are given an opportunity to do so. Although the overwhelming reason given for its usage is the tremendous efficiency it brings to a compounding pharmacy lab, moving forward we will begin to see that the overwhelming reasons to implement an EMP in your compounding lab are the consistency of results which result in predictable homogenous compounds, greater cleanliness in the process, and a more superior final preparation by creating both a hygienic compounding process and a hygienic environment for the dispensing of the compound by the patient, and probably most importantly providing a level of reproducibility unattainable by traditional methods giving the pharmacist, patient, physician, and regulatory body the confidence that quality assurance is at the greatest level achievable within the means of a compounding pharmacy.

HERE IS A GENERAL LIST OF THE SIGNIFICANT IMPROVEMENTS TO THE UNGUATOR OR EMP TECHNOLOGY

- Easier and more efficient loading of jars onto the machine. The improved technology of the lifting arm apparatus allows jars to be loaded and removed faster and easier. This will be a significant time saver over time, and add to the simplicity of machine usage.
- Quick-locking technology. Soon after the launch of the new machine models, pharmacists and their technicians will be able to take advantage of quick-locking technology with most of the Unguator EMP jars. This will provide even further time savings in the use of the Unguator EMP technology.
- The Unguator EMP model (the new version of the Unguator E/S) will have a much more compact size and reduced height. This reduced profile will allow the EMP (E/S) to more easily be placed in more confined spaces. The Unguator design team felt this was very important based on feedback of users especially those wanting to utilize the Unguator technology in powder and sterile hoods.
- Interfaces and improved mechanism. The new Unguator machines all include improvements throughout their construction based on feedback by customers over the many years the technology has been in use. These improvements, among other things, include a more component-based construction, which improves reliability and streamlines repairs; brushless motors, which are maintenance free and provide more than ample power for the most challenging mixing jobs seen in their current environments; and a more simple design that leads to a longer life, greater durability, and greater ease of use.
- Validation. All new Unguator models include state of the art validation routines which will greatly enhance the quality assurance of the pharmacy compounding lab in which they are utilized. The

software included in the Unguator Basic, EMP, and Pro will allow the Unguator machines to go through an initial validation upon receipt of the machine and to also go through periodic validation based on the policies and procedures of your lab. These validation routines correspond to *high quality standards* and will allow compounding labs to comply with validation requirements preferred by their applicable accrediting institutions and is in line with Current Good Manufacturing Practices.

- Integration. The newer models offer a level of integration not available in previous models. Not only is software included on board in the new machines to keep track of your compounds, but the new machines can be integrated with your desktop software to provide an even higher level of quality control.

HERE ARE THE NEW UNGUATOR OR EMP MODELS AND SPECIFIC IMPROVEMENTS TO EACH MODE.

GAKO UNGUATOR BASIC

The Gako Unguator Basic is the successor to the Unguator B/R. The Basic is the manual model of the Unguator technology. Although not

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used much in any significant topical compounding, the Basic model is very handy for quick powder and other mixes. The new Basic model increases the capacity possible to 500 grams. This new model also keeps track of the mixing time unlike the B/R, which is a great feature to allow greater documentation. The Basic carries the same design as the new Unguator EMP with a more technologically advanced interface and a smoother design making cleaning much easier.

GAKO UNGUATOR EMP

The Gako Unguator EMP is the successor to the Unguator E/S, the workhorse of the Unguator family for sure. The EMP model adds automation to the Basic, and like the E/S before it, allows the pharmacist or technician to leave the machine while it handles the mixing for them. The new EMP model adds all the new features we have talked about, and adds them in a new sleek and elegant design. In addition with both the Basic and EMP models, new and more powerful motors remove the requirement that the machines be left idle to cool down between mixes.

GAKO UNGUATOR PRO

The Gako Unguator Pro is the successor of the Unguator 2100 and combines the features of the 2100 as well as some advanced features made available through the Unguator Q. Like the 2100 the Gako Unguator Pro will mix quantities up to 1000 grams. The Gako Unguator Pro is much more technologically advanced than any other model with a very large high-resolution screen and the ability to even run software locally on the machine to track formulations and to provide various quality-assurance routines. The Gako Unguator Pro also includes a barcode scanner and keyboard making data entry into its provided software easy.

The Gako Unguator Pro is the most advanced mixing technology available for the typical compounding pharmacy lab and will make providing compounding services to your patients easy, efficient, and enjoyable.

Not only does the Gako Unguator Pro incorporate the quick-locking and fast-

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loading features mentioned previously, the Gako Unguator Pro also has the ability to interchange the lifting arm, allowing for future enhancements and attachments that Unguator users might request. In addition, the Gako Unguator Pro has been designed from the beginning to allow expansion up to 2000 grams of mixing capacity, a feature



that is currently planned for a year after the launch of the Gako Unguator Pro.

CONCLUSION

This article is not meant to say the methods typically used in a compounding pharmacy are not appropriate, but, rather, to point out that newer technology is available and might be preferable in order to provide a cleaner, more efficient, and more reproducible lab environment.

Although the Unguator is the only EMP and closed mixing system with the capability of some particle-size reduction implemented in the North American market, there are other technologies that either provides some alternative methods of mixing or complementary preparation of a formulation when mixing is required.

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The author is an ACA Fellow and was named legislator of the year in Oklahoma by the medical community in his second session in the legislature. RS Software, which was founded by the author, is the creator of Compound Assist. Health Engineering Systems, Inc., of which the author is President, is the North American distributor for Unguator technology. He is an active member of most pharmacy groups. 🇺🇸