gako PM140

The next step in compounding mixing technology

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Contents

1. The Importance of Standardized Processes in Compounding Pharmacy

Standardizing techniques and procedures is essential to guarantee high-quality and safe preparations in the compounding pharmacy. Compounded preparations without a standardized process may lead to potential changes in the active pharmaceutical ingredient (API) activity, influence the formulation aspect, and cause chemical alterations that potentially trigger reactions of different severity or inefficiency in treatments.[1,2]

According to the United States Pharmacopeia (USP)[3], the safety, quality, efficacy, and/or benefit of compounded preparations depend on a number of factors that should be monitored as part of the quality assurance process.

Those factors are:

- correct ingredients and calculations;
- accurate and precise measurements;
- appropriate formulation, facilities, equipment, and procedures (appropriate compounding equipment needs to be selected and inspected for cleanliness and correct functioning);
- and prudent pharmaceutical judgment.

To ensure accuracy and completeness, the compounder shall observe the finished preparation to ensure that it appears as expected, investigate discrepancies and take appropriate corrective action before dispensing the prescription to the patient.[3] In this sense, critical processes (including but not limited to weighing, measuring, and mixing) are verified by the compounder to ensure that procedures, when used, consistently result in the expected quality in the finished preparation.[4]

When a process is standardized[5]:

- Batch variation is reduced/eliminated;
- The quality of the product is assured;
- Regulatory risk (non-compliance) is reduced;
- Consistency of the compounding operation and process reproducibility is ensured;
- Quality Management System within the organization is ensured;
- Equipment maintenance is facilitated;
- Employee/compounder awareness is improved.

Health systems
are constantly challenged to ensure formulations
are prepared safely and accurately while complying with increasingly
complex regulations.

Standardization of processes
creates traceability and helps to eliminate or spot
formulation process deviations and errors.

Automated compounding solutions
provide pharmacists and technicians with the tools to improve
dose accuracy and product safety.
It also can reduce costs and enable compliance.

2. Critical Challenges in Focus: Mixing, Deaeration, and Melting

Mixing

Mixing is a pharmaceutical operation to achieve total homogeneity of the components in a formula: the essential condition for a final compliant product in terms of cream content is to be perfectly mixed.[5]

Mixing significantly affects the final characteristics of the compounded preparation, including physicochemical stability and dosage variation, compromising the safety and effectiveness of the treatment. Adequate mixing is crucial in preparing dosage forms within the compounding pharmacy.

Ensuring the efficiency and reproducibility of the mixing process is essential for reducing operational risks and batch variation and improving the pharmacy's quality management system.[5] Therefore, using equipment that can assist and enhance the safety and reproducibility of processes is highly important to pharmacists in their daily compounding practice[6].

This is also true for semi-solid formulations where the active ingredients are dose-dependent, especially hormones dispensed in dosing packages. Therefore, each dose should reproduce the remaining doses regarding active ingredient content.

Deaeration

Emulsion droplet/air interaction can have significant consequences for its stability.[7] Entrapped air increases the risk of dose inaccuracy in the final preparation, and it can alter the texture of an emulsion or gel, affecting its stability by adsorbing the emulsifier molecules at the air-liquid interface.[8] The final pH of the formula can also be impacted since the bubble formation interferes with fluid-flow patterns. Moreover, microorganisms grow in media with water and air, making most semi-solid dosage forms an ideal environment for their proliferation. Increased oxidation can also be seen due to the oxygen in the entrapped air.[9]

A substantial risk related to the presence of entrapped air as microbubbles or macrobubbles is the dosage variations they can cause, especially while working with small volumes, low dosages, or hormone replacement therapy (HRT) preparations.

A high degree of air entrapped in a cream may lead to changes in its density. Therefore, the precise dosing required for HRT can be compromised as it will affect the doses dispensed by the calibrated packaging, potentially causing underdoses and overdoses throughout the treatment.

This is also relevant for molded dosage forms that undergo melting during preparation, as in suppositories and vaginal inserts. Indeed, this is a phenomenon that creates the need for the calculation of displacement factors (df). The molds for those dosage forms contain a known, invariable volume. Still, the weight of the unit produced by the mold varies with the type of base used and the air incorporated throughout the compounding process. Also, the base is mixed with the drug, but the base and drug may have different bulk densities. Therefore, a low-density drug will displace a larger amount of the base than a similar weight of a higher-density drug – and this is, of course, also influenced by the density of the base, which is affected by the amount of air entrapped within it.[5]

Melting

The most commonly used method for pharmaceutical compounding of molded dosage forms is the Solidification Method: the excipient (the base mass) is melted, the ingredients in the formulation are added, and the mixture is poured into appropriate molds that have been greased with liquid petrolatum or mineral oil (for metal molds) – if packing molds (disposable molds) are used, they do not need to be greased.

During this process, time and temperature play an essential role. Although time can be easily controlled, temperature is a more complex parameter to standardize if the compounding facility does not possess a suitable device for this purpose. Using a water bath can help by limiting the maximum temperature reached. Still, fluctuations in the average temperature are also observed, making it challenging to keep the whole formulation at the same temperature. Also, the multiple steps in the process can lead to significant loss of materials throughout it.[5]

3. An All-in-One Solution: gako PM140

For pharmacists who are looking for a simple, fast, and affordable solution for mixing, deaeration, and melting, the **gako PM140** is a revolutionary device that combines those multiple functionalities to standardize the compounding process, ensuring safety, quality, and efficacy for compounded preparations while saving time and money for the pharmacy (Figure 1).

Moreover, it can be used on its own or in a combined workflow with other compounding equipment, such as the **gako EMP*** or other devices or molds required for the preparation of semi-solids or molded and melted solids dosage forms.

Figure 1. gako PM140 device.

3.1. Mechanism of action

Due to its ingenious mechanism, the preparation inside the PM jar (mixing jar) simultaneously spins and rotates around an axis in opposite planetary motion while keeping all the components at an angle of 40°. This promotes a centrifugal force caused by the rotational movement making particles in the mixture move toward the edges of the PM jar. As a result, the mixing process can be conducted in an enclosed environment without blades (Figure 2), reducing the number of items to be cleaned afterwards and enabling the pharmacist to **mix** and **deaerate** formulas within a simple one-step process (a process in less than 60 seconds). This centrifugal motion is accompanied by uniform and gradual heat release, facilitating the **melting** of substances such as suppository bases, gelatin bases, or gelling agents in the preparation (a process that requires around 15 minutes depending on the bases).

For optimal results, we are continuously developing suitable accessories including various PM jars and dispensers for the **gako PM140** (see Section 3.6. Accessories). The PM jars and dispensers provide a closed environment to reduce microbial contamination and eliminate spilling and spreading problems. They can be used in negative pressure cabinets to prevent hazardous drug exposure. The disposable ones that are also used as primary packages, help avoiding material loss that would otherwise occur during the transfer step from the preparation cup into the package.

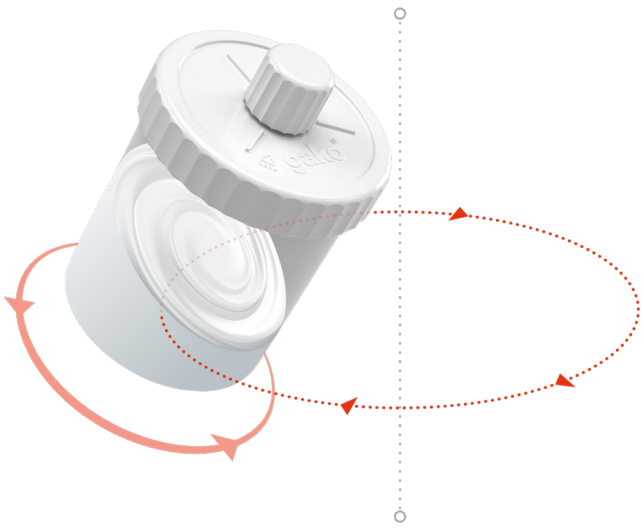

Figure 2. The working mechanism of gako PM140.

* **gako EMP** is a product line of fully automatic, semi-automatic, and manual versions devices, designed for mixing and the homogenization of semi-solid preparations (gels, creams, ointments, and suppositories) using blades.

3.2. Application and Uses

Mixing

gako PM140 is a user-friendly and practical device that allows the preparation of formulas in less than 60 seconds, in a closed mixing jar, with no need for mixing blades (Figure 3). The studies conducted by our laboratories show the content uniformity in all portions of the formulations produced. The standardized mixing allows for greater stability of emulsions, therefore eliminating formulation issues such as creaming, sedimentation, flocculation, and coalescence. An adequate homogenization also ensures correct rheological properties, such as the formulation's viscosity and flow.

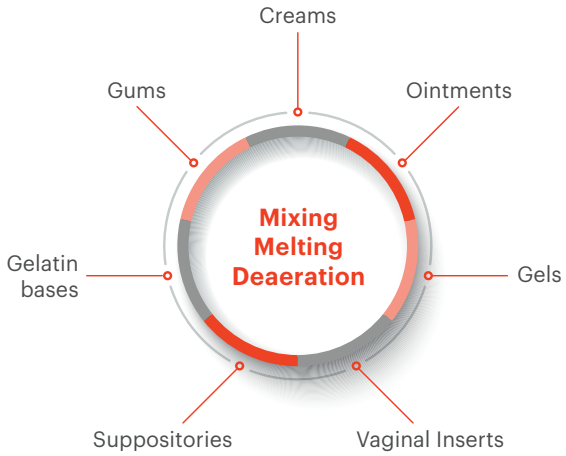

Figure 3. Mixing process using the gako PM140.

Deaeration

gako PM140 deaerates emulsions and gels in just 45 seconds, ensuring the removal of macrobubbles from those formulations (Figure 4).

Melting

gako PM140 can melt gelatin, suppository, and vaginal inserts bases in one simple step: the bases can be placed together with the APIs and other necessary ingredients in the PM jar (Figure 5).

Figure 4. Deaeration process using the gako PM140.

Figure 5. Melting process using the gako PM140.

3.3. Key Features

Single-Step Process

gako PM140 combines mixing, melting, and deaeration processes in a single step. Therefore, it simplifies the compounding of pharmaceutical preparations and saves time while ensuring high-quality formulations. As demonstrated in studies conducted by our scientific expert team, the temperature rise is limited to 45°C, making it suitable for most heat-sensitive ingredients.

Time-Saving

The high mixing speed of **gako PM140** is fixed to 2800 rpm, allowing the preparation of formulations in less than 60 seconds.

Dosage Accuracy

In volume-dependent doses, as in HRT creams, a reliable mixing process that deaerates the formulation improves API distribution and ensures dosage accuracy for each application.

Material-Loss Prevention

In traditional mixing processes, material loss occurs during the transfer to the final package after mixing. Even if the exact amounts are calculated and weighed, the compounded preparation is never completely transferred from the mortar into the package, especially when working with semi-solid dosage forms. To prevent material loss, the **gako PM140** is designed to mix the formulation in a disposable PM jar, also used as a final package to be delivered to the patient.

Conservation of Resources

The **gako PM140** contributes to water conservation, as it does not require subsequent washing and rinsing steps of spare parts such as blades and mixing rods.

Low-Maintenance

The **gako PM140** is distinguished by quality materials that allow for a low-maintenance and durable service, improving cost-efficiency. Due to its compact and functional design, the device can be easily integrated into lab furniture or used on the workbench. It also eliminates issues when compounding colored ingredients, such as coloring the blades or wearing them out by changing color and avoiding cross-contamination in a hormone preparation through the edges.

Compounding Hazardous Drugs

The term "hazardous drug" (HD) was first described by the American Society of Health-System Pharmacists (ASHP) in 1990 and has also been used by Occupational Safety and Health Administration (OSHA) for compounds that display the following characteristics: genotoxicity; carcinogenicity; teratogenicity or loss of fertility; and severe toxic manifestations at low doses in experiments with animals or treated patients. An API is considered hazardous if it features one or more of these characteristics, and new APIs with structure and toxicity profiles that mimic those of hazardous APIs are also classified as HDs.

According to the United States Pharmacopoeia (USP), pharmacists can be potentially exposed to HDs while compounding when:

- Weighing or mixing components;
- Crushing or splitting tablets or opening capsules;
- Pouring oral or topical liquids from one container to another;
- Constituting or reconstituting powdered or lyophilized HDs;
- Withdrawing or diluting injectable HDs from parenteral containers;
- Expelling air or HDs from syringes;
- Contacting HD residues present on Personal Protective Equipment (PPE) or other garments;
- Deactivating, decontaminating, cleaning, and disinfecting areas contaminated with or suspected to be contaminated with HDs;
- Maintenance activities for potentially contaminated equipment and devices.

gako PM140 decreases the risk of exposure to HDs as it works in a closed environment provided by the PM jars. Additionally, the PM jars can be placed in negative pressure cabinets, which increases safety for the compounding of HDs.

3.4. Instructions for Use

The **gako PM140** enables the pharmacist to melt, mix, and deaerate formulas within a simple one-step process, as easy as just pressing one button: after placing the formulation ingredients into the PM jar, setting the time, and pressing the start button, the device is ready to operate the mixing process. Figure 6 shows how straightforward the process is and how the device can be used from multiple starting materials and combined with other devices to achieve optimal results. Table 1 also shows how the **gako PM140** can help standardize the compounding processes.

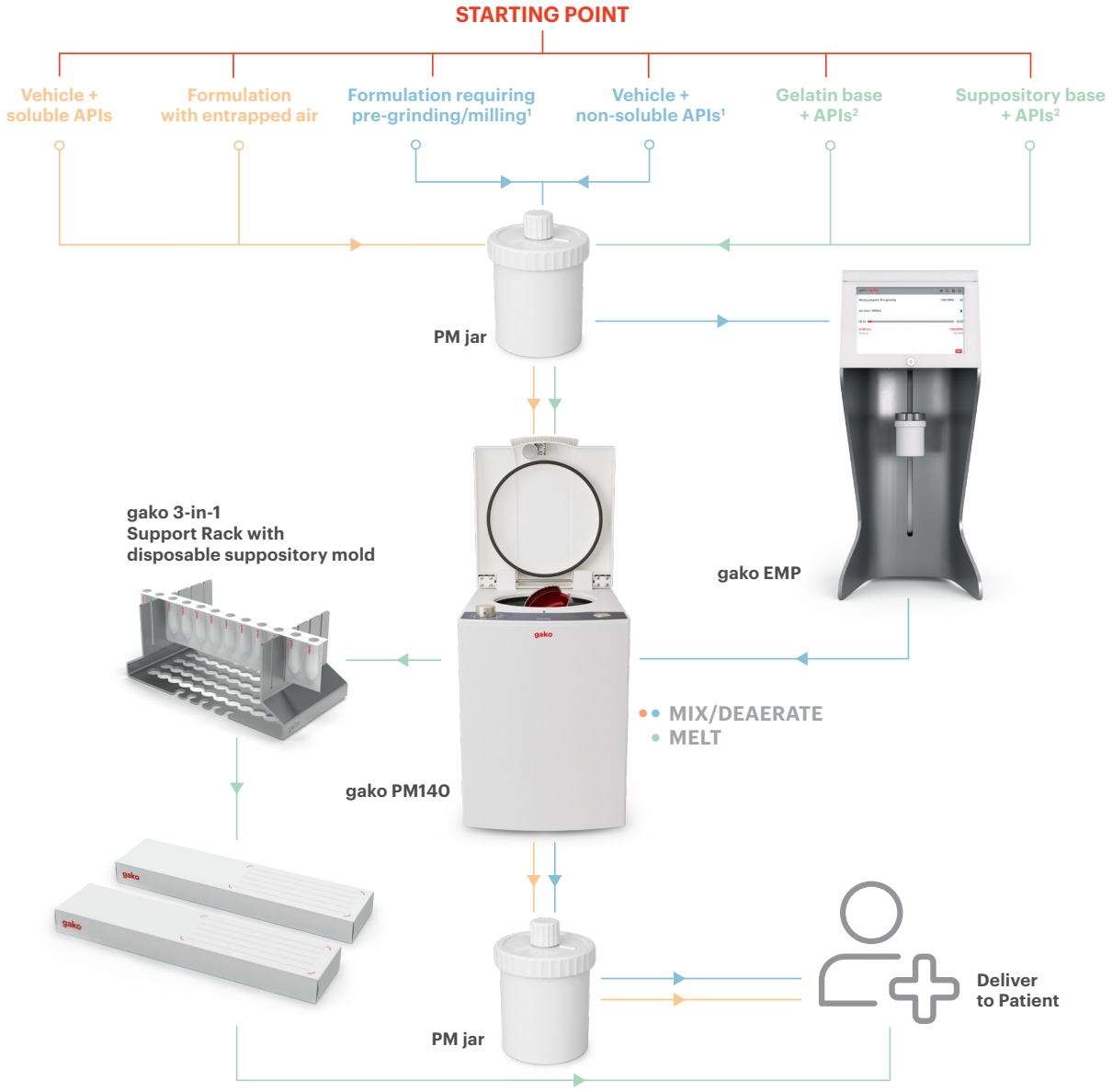

Figure 6. Workflow for gako PM140 used standalone and in combination with other devices.

1. If the formulation contains non-soluble APIs, the use of gako PM140 together with gako EMP is recommended. Primarily, the gako EMP can pre-grind and disperse all the components in the base. Afterward, the formula can be placed into gako PM140 for final mixing and deaeration. Both processes can be carried out using the same PM jar, which can also be the dispensing package.
2. For suppositories and vaginal inserts, gako PM140 can melt substances up to 45°C within a simple one-step process and is suitable for mixing most heat-sensitive ingredients. gako 3-in-1 Support Rack is also available; together with gako Vaginal Insert & Suppository Strips, a single-use mold used as final packaging, so the pharmacy can have a practical solution to combine molding and packaging functions.

NOTE: The gako EMP devices can prepare ointments, creams, and gel vehicles of up to 2.000 mL at once in a homogeneous formulation (500 mL for gako EMP Basic and Standard, and 2.000 mL for gako EMP Pro). This makes it an ideal choice for producing vehicles/bases or large batches to be later split into smaller amounts.

Table 1. Critical processes in preparation of compounded formulations and the role of the gako PM140.

Critical process steps	Variable to monitor	Possible to standardize with gako PM140?
Mixing/homogenization	Time Speed	Yes
Melting/heating	Time Temperature	Yes
Addition ingredients incorporation	Mixing method Time Speed API accuracy of dose	Yes
Packaging	Closure of the jar Absence of reactions with formulations	Yes (with the PM jars)

3.5. gako PM140 standardized protocols

3.5.1. Mixing with low-Viscosity Bases

The mixing process of ingredients with low-viscosity bases is summarized in Table 2.

Table 2. Mixing protocol for low-viscosity bases using the gako PM140.

Formula type	Emulsion + Liquid API	Emulsion + Powder API*
Jar	gako PM jar 125 mL HV+LV	gako PM jar 125 mL HV+LV
Quantity	50 g to 125 g (max)	50 g to 125 g (max)
Time	30 seconds	45 seconds
Temperature	The maximum temperature reached is 25 °C	The maximum temperature reached is 25 °C

3.5.2. Mixing with High-Viscosity Bases

Some creams may present a high-viscosity characteristic, e.g., transdermal creams in general, such as Pentravan®. Those may require an extended mixing time, as described below. This mixing process is summarized in Table 3.

Table 3. Mixing protocol for high-viscosity bases using the gako PM140.

Formula type	Pentravan® + Liquid API	Pentravan® + Powder API*
Jar	gako PM jar 100 mL HV	gako PM jar 100 mL HV
Quantity	50 g to 100 g (max)	50 g to 100 g (max)
Time	30 seconds - 1 minute	2 - 3 minutes
Temperature	The maximum temperature reached is 25 °C	The maximum temperature reached is 25 °C

3.5.3. Deaeration

The deaeration process of formulations with entrapped air is summarized in Table 4 and Figure 6

Table 4. Deaeration protocol for formulations containing entrapped air using the gako PM140.

Formula type	Gel + Liquid API	Gel + Powder API*
Jar	gako PM jar 100 mL HV	gako PM jar 100 mL HV
Quantity	50 g to 100 g (max)	50 g to 100 g (max)
Time	30 seconds	45 seconds
Temperature	The maximum temperature reached is 25 °C	The maximum temperature reached is 25 °C

3.5.4. Melting

The melting process is a simple and effective way to melt bases such as vaginal insert bases, suppository bases, or other bases (gelatin or gum) that require melting, allowing the pharmacy to melt formulas in a closed and safe environment. This mixing process is summarized in Table 5.

Table 5. Melting protocol for vaginal inserts, suppository bases, or other bases (gelatin or gum) that require melting, using the gako PM140.

Formula type	Supposiblend™ + Liquid API	Supposiblend™ + Powder API*
Jar	gako PM jar 125 mL HV+LV	gako PM jar 125 mL HV+LV
Quantity	30 g to 50 g (max)	30 g to 50 g (max)
Time	13 minutes	15 minutes
Temperature	The maximum temperature reached is 35 °C	The maximum temperature reached is 37 °C

* When a powder API is used in the gako PM140, we recommend using a levigating agent to facilitate the incorporation of the APIs. It can be pre-mixed together, forming a paste, or the levigating agent can be placed above the powder, covering it completely. It is crucial to keep in mind the compatibility of the components with the base. This process is necessary before starting the gako PM140 to avoid an accumulation of the powder in the bottom or the top of the PM jar.

3.6. gako PM140 Accessories

gako PM jar 100 mL HV is a sterile and disposable jar composed of polypropylene, and it is specifically designed to be used in the deaeration and mixing processes of gels, creams, and ointments. Although its capacity is up to 100 mL, the internal nominal volume is 140 mL.

This extra volume is necessary to allow the particles to move through the process, and promote its features. The PM jar presents a movable bottom. After the preparation, the remaining volume can be eliminated by pushing the bottom upwards, reducing air contact.

It is also compatible with **gako EMP** devices, enabling it to be used with low-soluble APIs and to prepare suspension formulas. It, therefore, eliminates the need to transfer the compound from the EMP jar to the **PM jar 100 mL HV**. Since the jars are made of a disposable material, they can also be used as a primary package to deliver to the patient, reducing the tools to be cleaned, saving time, and avoiding material loss during the transfer phase.

The **gako PM jar 125mL HV+LV** is a disposable jar with a fixed bottom, designed to be used mainly for the melting of the suppository preparation, and mixing more fluid formulas – but it can also be used for other preparations like creams, ointments, and gels.

The capacity of this jar is also 125 mL with a 180 mL nominal volume. When the device is operated in room temperature, the content can reach up to 40 °C. In case the prescription requires higher temperature, the external heat can be applied to the **gako PM jar 125 mL HV+LV**, up to 80°C by using a hot water bath. Table 6 lists the differences and applications for each jar.

Table 6. Comparing gako PM jars.

Accessory	gako PM jar 100 mL HV	gako PM jar 125 mL HV+LV
Internal Nominal Volume	140 mL	180 mL
Maximum capacity for Mixing	100 mL	125 mL
Bottom	Movable	Stable
Sterility	STERILE|EO*	STERILE|EO*
Applications	Deaeration Mixing	Deaeration Mixing Melting
EMP Suitability	Suitable	Not suitable
Mixing Period	Up to 1 minute	Up to 15 minutes for melting Up to 1 minute for mixing and deaeration
Suitable Dosage Forms	• Ointment • Cream • Gel	• Ointment • Cream • Gel • Lotion • Suppository • Insert
Usability as Dispensing Primary Packaging	Applicable	Applicable

* **STERILE|EO**: Sterilized with ethylene oxide.

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