WetMill Compact

Planetary colloidal milling solution for pharmacies

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1. Introduction

Compounding personalized medicine can be defined as the combination or mixing of pharmaceutical ingredients to create specific treatments according to individual patient needs. This can be achieved through compounding pharmacies and their ability to customize dosage, pharmaceutical forms, ingredients and make specific adjustments for special groups, such as pediatric, elderly, or hospitalized patients.[1,2]

The acceptability of a pharmacological treatment often depends on it being formulated in a pharmaceutical form that is suitable for the patient. Unfortunately, commercially available pharmaceutical specialties do not always meet the specific needs of certain groups of patients, for example, those who have difficulty swallowing tablets and capsules, or patients that must receive their medication through a nasogastric or gastrostomy tube.[2,3] One of the strategies applied to meet these specific needs is through extemporaneous preparations – converting solid forms to oral liquid suspensions.[4]

2. Extemporaneous Oral Liquid Preparations

The compounding process of extemporaneous oral liquid preparations, in general, involves two steps: (1) the reduction of tablets or capsule contents into fine particles (when no raw pharmaceutical material is available) and (2) the use of these powders in the compounding of a liquid formulation by adding vehicles and pharmaceutical excipients such as flavors, sweeteners, viscosity enhancers, and antimicrobial preservatives.[4,] The reduction of particles is usually made using a variety of dry-grinding techniques, such as the use of mortar and pestles, grinders, and devices that "mash" tablets in plastic bags. These grinding techniques lack reproducibility and often produce powders with uneven particle sizes, that are less suitable for the formulation of physically stable liquid preparations, and may also result in particles or crystals by precipitation, leading to blockage of nasogastric tubes. The extemporaneous preparations can be applied to all types of pharmaceutical ingredients, hazardous or non-hazardous. When compounding with hazardous drugs (HD), drugs with low therapeutic index, and also high allergenic drugs, in addition to the correct reduction of particles and stability of the formulation, cleaning of used utils is cumbersome and, if not done properly, might lead to cross-contamination.[4,5]

2.1 Personalizing Extemporaneous Oral Liquid Preparations

One of the reasons to compound extemporaneous preparations, is the small availability of certain pharmaceutical specialties to some patient groups, as discussed before. For children, for example, there is not a large and varied market of dosages available as there are for adults, and compounding oral liquid formulations easily address dose variations required for them.[4] Elderly patients may take at least one medicine daily, while others may take up to five different medicines simultaneously due to hypertension, diabetes, cardiovascular alterations, and others.[6,7] Both pediatric and elderly patients have difficulty swallowing tablets and capsules, and the need for dose adjustments and a suitable pharmaceutical vehicle can be addressed by compounding extemporaneous preparations for day-to-day treatments.

While compounding an extemporaneous preparation, the pharmacist must ensure that all technical and chemical requirements are compliant, to keep both treatment efficiency and patient safety at a high level.

2.2 Compounding with Hazardous Drugs

During day-to-day care inside compounding pharmacies, hospitals and special care clinics, pharmacists frequently need to prepare formulations containing HD. According to the American NIOSH (National Institute of Safety and Health), a drug is classified as hazardous if displays one or more of the following characteristics: genotoxicity, carcinogenicity, teratogenicity, or serious organ or other toxic manifestation at a low dose. Airborne particles can be created while compounding with such drugs, exposing the pharmacist or technician constantly to these hazardous particles.[8,9]

Frequent exposure to HDs in the workplace can result in several adverse health effects. Various studies have shown that effects can include skin rash, adverse reproductive outcomes (including infertility, abortions, and congenital malformations), ocular damage, flu-like symptoms, and headache.

Even leukemia and other types of cancer have been associated with the exposition to HD.[9] To minimize exposure and associated risks, handling of HDs should follow specific policies and procedures. This can be done through primary prevention measures such as engineering controls, administrative controls, and personal equipment.[8,9]

Safe handling of HDs has been an increasing concern for compounding pharmacies. Nonetheless, there is a need for compounding techniques that can provide safety to the healthcare worker and the patient and deliver high-quality formulations.[8,9]

3. WetMill Compact

The **WetMill Compact** is an automated compounding device, developed to provide a safe and validated alternative to the dry-grinding process to compound extemporaneous oral liquid preparations, through the use of an innovative wet milling process. In addition, the device offers a complete solution for compounding HDs through a completely enclosed and cross-contamination-free system, converting tablets or whole capsules into homogeneous oral liquid formulations, ideal for patients with special needs.

3.1 The Industry Inside a Bottle

In the pharmaceutical industry, the colloid mill has been widely used to reduce the particle size of solids or liquids, to produce homogeneous suspensions or emulsions. It works on the rotor-stator principle: a rotor turns at high speed and a high level of hydraulic shear is applied, disrupting and breaking down the structure and promoting the dispersion of particles in the liquid.[10,11] Even though they are highly effective, colloid mills are large, heavy, and expensive machinery, only suitable for one preparation at a time. They are ideal for large industrial processes, but less suitable for small compounding pharmacies.

WetMill Compact utilizes the same principles as a colloid mill, but on a much smaller scale through its functional patented milling bottles. Specially designed with an abrasive (rough) surface on the interior, the milling bottles produce uniform particles that are well suited for the compounding of liquid pharmaceutical formulations. The bottles are disposable and present a 3-in-1 solution: they can be used to compound, store, and dispense the medication. The **WetMill Compact** can produce up to 4 different formulations at a time, resulting in a time and cost-saving process.

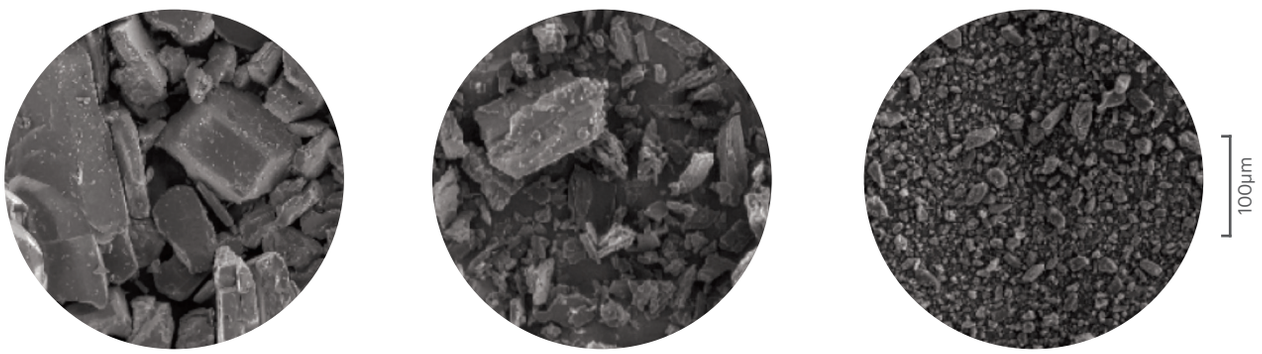
The abrasive surface of the patented bottles, combined with a high-speed planetary rotation cycle, results in fine, uniform, and homogeneous formulations, replicating the process applied to the pharmaceutical industry on a smaller scale.

3.2 Benefits and Advantages

› The 3-in-1 concept

› Reduction and homogenization of particles

A comparison of Rifampin particles from whole powder compared to manual grinding (mortar and pestle) and wet milling with the **WetMill Compact** system.



A. Whole Powder

B. Manual Grinding

C. WetMill Compact

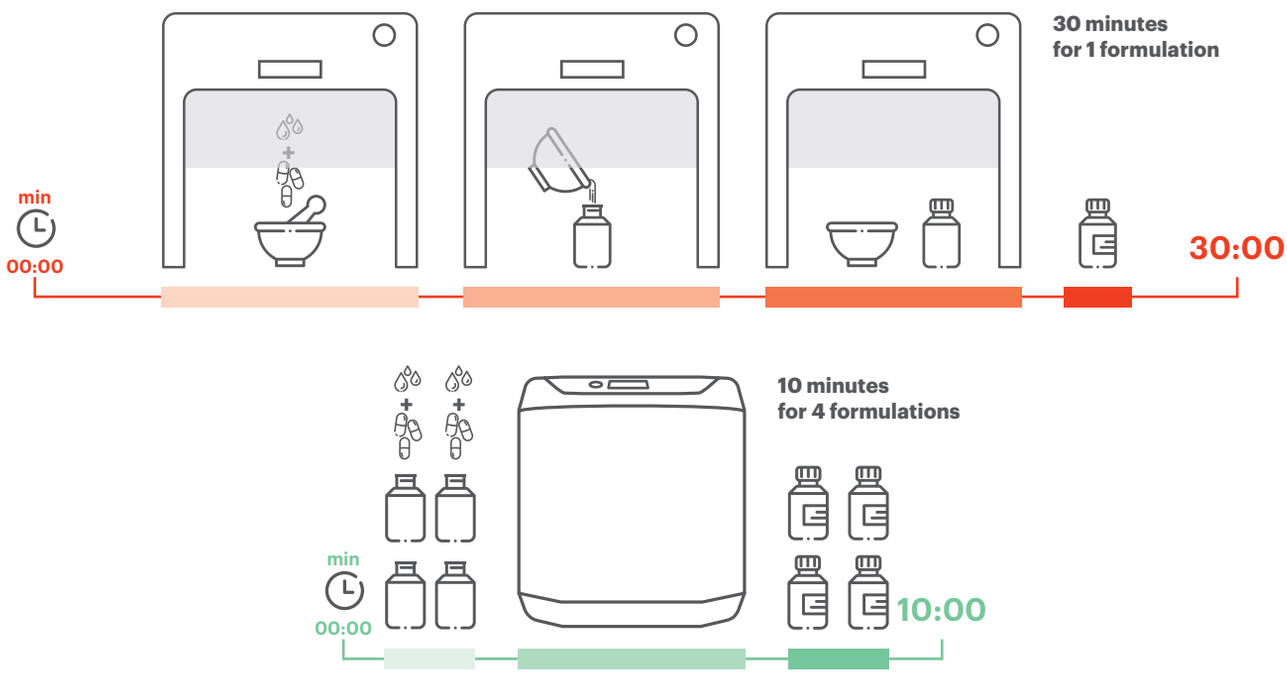
› Validated cross-contamination-free system

Safety for the patient
The cross-contamination risk is eliminated by the system by using a single bottle for compounding, storage, and dispensing the medications. No extra cleaning is required after the operation.

Safety for the pharmacist
The aerosolization of particles is contained by the use of enclosed bottles during the entire compounding process, avoiding direct exposure of personnel to substances being prepared.

› Time-saving

The traditional techniques for compounding extemporaneous preparations from tablets, whole capsules, or bulk powders, either hazardous or non-hazardous ingredients, require several security measures such as adequate personnel protection, safety cabinets, and careful cleaning after compounding. The manual grinding process, depending on the tablet size and format, can take up to 30 minutes to be properly ground, and still can present uneven particle size.



4. Scientific Background

Several and studies were undertaken with the **WetMill Compact**, to prove the efficacy and safety of the device during compounding. The main objective was to validate the closure integrity of the device during milling, the machine's capacity to create fine, uniform particles, and the content uniformity of the final compounded formulation.

4.1 Closure Integrity

4.1.1 Aerosolized Powders

To validate the closure integrity of the **WetMill Compact** during compounding, a study was undertaken to verify the absence of aerosolization of powders. Methylene blue and rifampin were selected as test compounds for their strong chromophore properties. The samples were submitted to ten 10-minute cycles (to provide a stress condition), and after the test, the device was swabbed with methanol. The results showed that no methylene blue or rifampin was detected on the surface of the bottles or the device under all test conditions, showing that there is no risk of cross-contamination while compounding different formulations inside the device.

4.1.2 Thiamine HCl

A second test was performed to confirm the closure integrity of the **WetMill Compact**. In this case, Thiamine HCl was used as a model compound. Four bottles (in triplicate) filled with 25 mg/mL Thiamine HCl were mixed for 30 minutes in total. The surface of the bottles and the interior and exterior of the machine were swabbed and analyzed for traces of Thiamine HCl by a validated HPLC with a detection limit of 0.02 µg/mL. The results showed that there was no presence of thiamine in any of the analyzed samples.

The studies performed show that the **WetMill Compact** has excellent closure integrity and can therefore be used to compound hazardous medication in a safer way than when performed by manual techniques.

4.2 Uniformity of Particles

Enteral Feeding Tube Administration[12]

Blockage of medical tubes during the administration of oral suspensions is a widespread problem leading to patient discomfort, additional costs, and even increased patient risk.[13] A study was undertaken to evaluate the impact of the method of suspension preparation of rifampin capsules on nasogastric tube clogging. Suspensions were prepared using (A) mortar and pestle or (B) the **WetMill Compact** (pre-alpha version). The injectability of the suspension through the nasogastric tube was measured *in vitro* to determine which suspension vehicle and preparation method helped to maintain tube patency best. Suspension vehicles used were:

1. Water;
2. Simple syrup;
3. Sugar-free vehicle for oral suspension;
4. A mixture of 2 vehicles for oral suspension;
5. Single vehicle for oral suspension.

The study demonstrated that preparing rifampicin suspensions from capsules using the wet milling technology produced smaller, more uniform particle sizes with greater resistance to sedimentation. **Figure 1** shows polarized (left) and electronic (right) microscopy photomicrographs of the formulation particles.

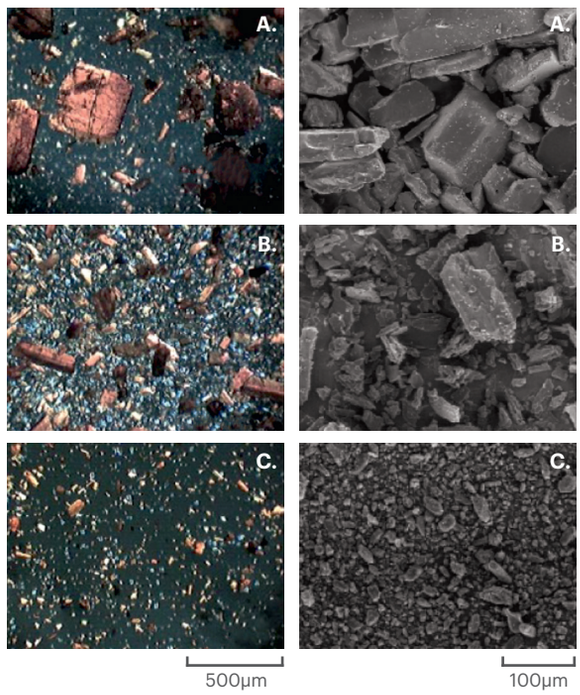


Figure 1. *(left) Polarizing photomicrographs of rifampin crystals of A. Capsule powder; B. Capsule powder suspended in water using mortar and pestle; C. Capsule powder suspended in water using wet milling. (right) Electronic photomicrographs of rifampin powder suspended in water A. Unmixed; B. Mixed with mortar and pestle; C. Mixed with wet milling.*

When an oral suspension vehicle was added, nasogastric tube patency was maintained for 7 days, with no tube blockage observed in comparison to mixing with mortar and pestle. Suspensions in these vehicles showed good flow through the syringe and very small (8F) nasogastric tubes (**Table 1**).

Table 1. *The injectability of the suspensions through an 8F nasogastric tube measured with a syringe pump every 24 hours for seven days. Tube blockage is demonstrated by (x), and successful flow is demonstrated by (✓).*

Formulation	Method	Days							
		0	1	2	3	4	5	6	7
1	A	✓	✓	x	x	x	x	x	x
	B	✓	✓	✓	x	x	x	x	x
2	A	✓	✓	✓	x	x	x	x	x
	B	✓	✓	✓	✓	x	x	x	x
3	A	✓	✓	✓	✓	✓	✓	x	x
	B	✓	✓	✓	✓	✓	✓	✓	✓
4	A	✓	✓	✓	✓	✓	x	x	x
	B	✓	✓	✓	✓	✓	✓	✓	✓
5	A	✓	✓	✓	✓	✓	✓	x	x
	B	✓	✓	✓	✓	✓	✓	✓	✓

4.3 Content uniformity

4.3.1 Compounding of an oral suspension of clonidine hydrochloride 20 µg/mL for neonatal patients using tablets

In a study undertaken to demonstrate the efficiency of the **WetMill Compact** in formulating a low concentration formula for neonates, whole tablets of clonidine hydrochloride and water were added in the milling bottles, and a 10-minute cycle was performed. The results showed that the content uniformity of the formulation was within 1% of the label claim (%RDS = 0.84%). The long-term stability results were within 5% of the label claim at room temperature.

4.3.2 Compounding oral liquid formulas of two hazardous drugs (tacrolimus 1 mg/mL and hydroxyurea 100 mg/mL), using unopened capsules

A study was undertaken to demonstrate the efficiency of the **WetMill Compact** in formulating hazardous drugs. Whole capsules of tacrolimus and hydroxyurea were compounded into 1 mg/mL and 100 mg/mL oral liquid suspensions, respectively. A 32-minute cycle was used. The results showed that the dose uniformity of the formulations was within 7% of the label claim for the tacrolimus (%RDS = 5.5), and within 2% for the hydroxyurea (%RDS = 1.1). Again, long-term stability results were well within specifications, with 3% for the tacrolimus and less than 8% for the hydroxyurea at room temperature.

4.3.3 Content Uniformity using a high-dose formulation of paracetamol and SyrSpend® SF PH4

The addition of a suitable suspending vehicle is essential to maintain good content uniformity throughout the patient's therapy. SyrSpend® SF PH4 is a ready-to-use suspending vehicle with unique suspending properties and excellent compatibility that allows for compounding safe preparations for patients. In this study, the content uniformity was analyzed using a high-dose paracetamol formulation (50 mg/mL, from bulk powder). Following a full 10-minute cycle, 6.5 g of SyrSpend® SF PH4 dry was added and homogenized by shaking the bottle thoroughly for 1 minute. In total, 8 samples were prepared. Samples were stored and resuspended after 14 days. The results showed that the formulated paracetamol suspension displayed excellent uniformity of content, within 5% of the label claim (VA = 6.7).

These studies demonstrate the effectiveness of the **WetMill Compact** when compounding oral liquid formulas using whole capsules and tablets. The data highlight the excellent content uniformity, for both low and high dosed compounded suspensions, while eliminating the variability of manual labor.

5. Vehicles and Adjuvants

The **WetMill Compact** can compound formulas using various diluents. Water is the most efficient in terms of energy transfer for wet milling and is therefore recommended. Following the suspension preparation with water, it is advised to add a suspending agent to allow for proper suspension and hence optimal patient dosing and safety. SyrSpend® SF PH4 NEO (preserved), SyrSpend® SF PH4 dry, or SyrSpend® SF Alka are globally available, commercial vehicles that will allow for optimal suspending of the milled tablets or capsules. Also, SyrSpend® SF has proven physical-chemical stability with over 100 different Active Pharmaceutical Ingredients in 150 different formulations. When combining the WetMill Compact technology and SyrSpend® SF, we ensure the highest quality standards in all formulations prepared, with validated stability and content uniformity in all preparations.

Even distribution of the milled particles, the proven closure integrity of the system, and the proven Content Uniformity when combined with SyrSpend® SF, make the **WetMill Compact** an excellent alternative to traditional procedures used to compound hazardous medications while better protecting pharmacy staff.

Additionaly, the following medications have been tested with the **WetMill Compact**:

Azathioprine (from tablets)	Hydroxyurea (from whole capsules)	Sildenafil
Amlodipine (from tablets)	Lisinopril	Spironolactone (from tablets)
Baclofen	6-Mercaptopurine (from tablets)	Tacrolimus (from whole capsules)
Clonidine	Methotrexate (from tablets)	Topiramate (from tablets)
Dexamethasone	Metronidazole	Ursodiol
Haloperidol	Rifampin	

When compounding with whole capsules or tablets, a wide range of formulations has been tested, showing the capability of the technology to compound up to 100 tablets in one bottle. This number can vary according to the size and strength of the tablet used as a medication source, but this shows that the **WetMill Compact** is suitable for compounding most prescribed medications.

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Fagron BV
Lichtenauerlaan 182
3062 ME Rotterdam
The Netherlands

T +31 88 33 11 288
F +31 88 33 11 210
www.fagronlab.com