



## InvoMatic

Advanced 3-axis mixing technology  
for compounding



## 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, and ingredients, making specific adjustments for special groups, such as pediatric, elderly, or hospitalized patients.<sup>1</sup>

The combination of ingredients and the customization of treatments are possible thanks to what can be called pharmaceutical operations. These operations are of great importance for the quality of the final product, and can be divided as physical (i.e. dissolution, distillation, drying) or mechanical (i.e. grinding, mixing).<sup>1</sup> One of the most important and largely applied operation in every type of compounded formulation is the mixing process.<sup>2,3</sup>

A mixture can be defined as the homogeneous association of several substances – solids, semi-solids, or liquids – and the quality of the mixture plays a significant role in the final product, directly influencing the efficacy and even the safety of treatments.<sup>4</sup> In a compounding pharmacy, several methods and equipment can be applied for mixing ingredients, such as the use of mortar and pestle, magnetic or electric agitators, and large-scale mixers like the V or Y-shaped mixing systems, planetary and tumbler mixers, among other kinds.<sup>1</sup>

## 2. Powder Mixing

The most common – and one of the most challenging operations in the compounding pharmacy is powder mixing. The main challenge rests on understanding the particularities of the many different ingredients, and how they will behave together inside of the same mixture. It is common that, for physical-chemical reasons, a pharmaceutical powder mixture contains up to 20 different ingredients to meet the acceptable quality standards of the final product.<sup>2,5</sup>

Many factors can influence the powder mixing efficiency. The flow characteristics of the ingredients, particle size and shape variations, particle density, cohesivity, hygroscopicity, and hardness are some of the physical parameters that can directly impact the quality of the mixture.<sup>2,6</sup> If these particularities are not taken into consideration previously, the results can be the agglomeration of particles and the uneven distribution of ingredients leading to a lack of dose uniformity in the formulation.<sup>2</sup>

The adequate choice of the mixing technique and equipment can play an important role in the stability and quality of the mixture. There are different categories of mixing equipment, which can be classified either as segregating mixers, which work mainly under diffusive mechanisms, moving the material inside of a container, or as less segregating mixers, which work under convective mixing mechanisms with internal rotors.<sup>2,7</sup>

The segregating mixers, or so-called diffusive mixers, are widely used in the pharmaceutical industry for powder or granular mixing. They are easy to operate and present a good solution for shear-sensitive ingredients, that can be affected by the rotor movement of the convective mixers. This category of mixer also does not generate temperature during the mixing process, another advantage for thermo-sensitive ingredients.<sup>8,9</sup>

The most known type of diffusive mixer is the V or Y-shaped blender but, although well established, these devices are more suitable for large-scale production, and require high standard cleaning operation after use, since their parts are permanent, making them less favorable for small batches compounding preparations.<sup>9</sup> There is a growing trend and necessity for smaller-scale mixing devices, that are safe and validated for the pharmaceutical compounding market, to provide both efficiency and high-quality standards to personalized treatments.

### 3. InvoMatic

**InvoMatic** is an automated mixing system developed to produce highly homogeneous mixtures at controlled time and speed. **InvoMatic** works in a 3-axis movement, combining the principles of the oloid and inversion mixing, creating a unique 3D-movement cycle, that allows a complete diffusive mix. Also, **InvoMatic** is equipped with a digital system that allows the pharmacist to choose their mixing cycles according to their needs, creating multiple combinations to fit the formulation characteristics, achieving easy and efficient reproducibility.



Figure 1. The oloid.



### 3.2 The diffusive mixing method

The diffusive mixing method consists of particles moving randomly inside of a vessel, under influence of gravity to impel the flow, causing the particles to roll to the opposite side of the vessel, therefore producing homogeneous mixtures.

The mixing process of **InvoMatic** is performed inside of any vessel available in the compounding pharmacy. This is a great advantage for containing the materials during the process, ensuring an enclosed and safe environment during the mixing cycle also with hazardous preparations, and avoiding the necessity of extra cleaning operation after every use. Just change the vessel, and the device is ready for the next cycle.

Depending on the properties of the substances being mixed, extra tools can be added inside of the vessels during mixing, such as porcelain or ceramic spheres, to avoid particle agglomeration and create even particle size in the formulation. **InvoMatic** can operate with a mixing speed from 0 to 100 RPM, and a mixing time from 0 to 99 minutes, creating multiple combinations to fit the formulation properties. The mixing arm is capable of holding vessels from 30 mL to 1.000 mL (average). **InvoMatic** is suitable for the complete mix of solids, but also liquids, homeopathic preparations, and impregnation of globules and granules.

The **InvoMatic** is the evolution of powder and liquid mixing in the compounding pharmacy.



### Advantages

- Unique 3-axis mixing robotic arm
- Reproducibility and speed
- Automated process
- Validated mixing process
- GMP and GLP compliant
- Safe for hazardous preparations
- Reliability
- Any vessel, any volume
- No cleaning after mixing

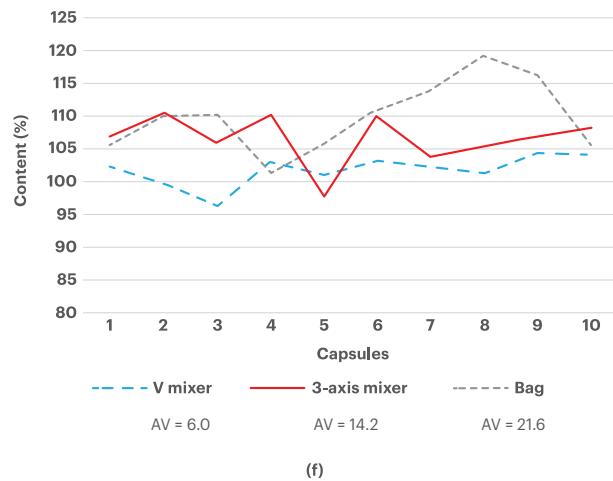
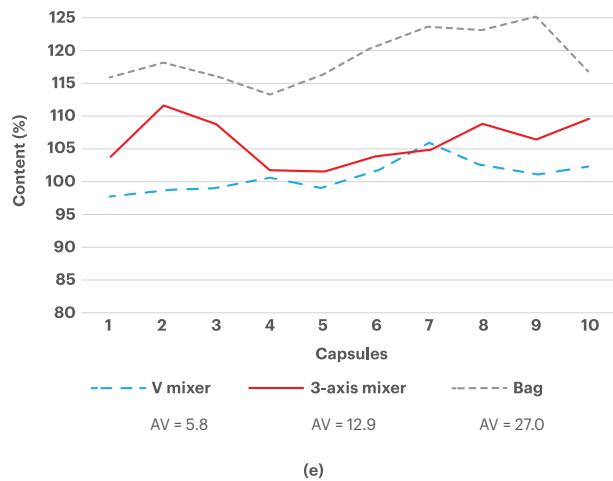
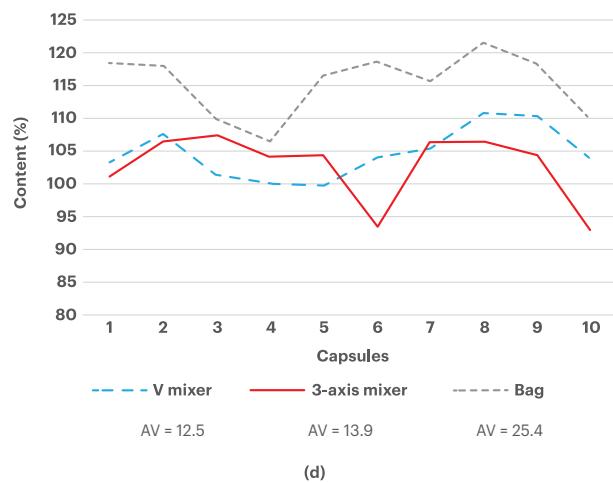
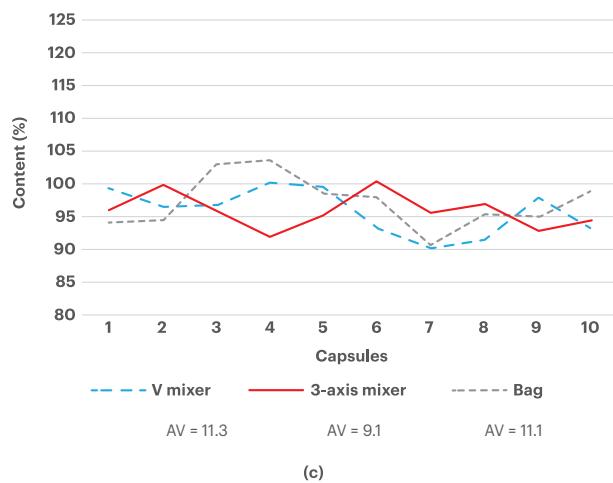
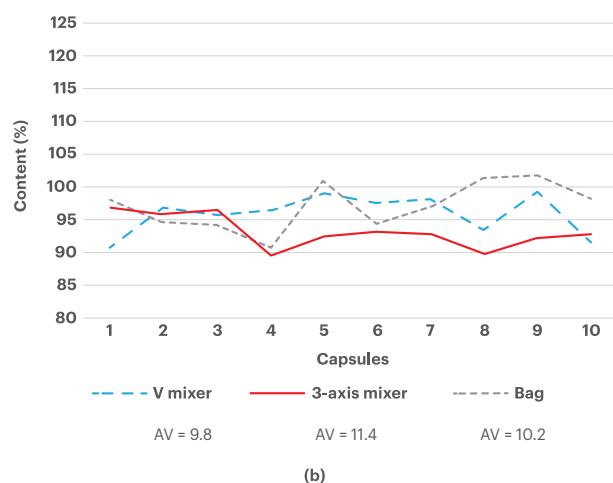
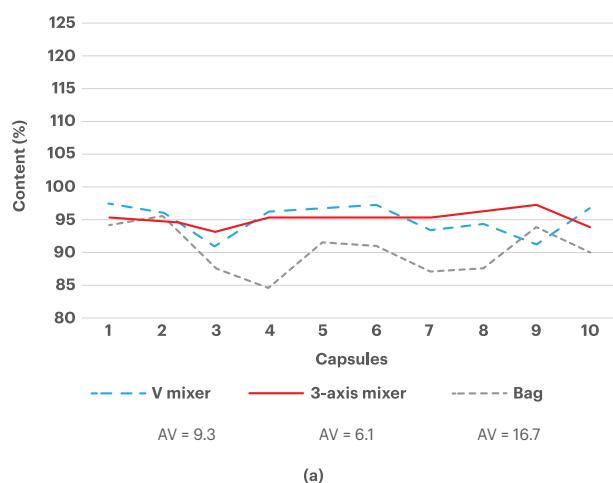
## 4. Scientific Background

### 4.1 Content Uniformity

To evaluate the mixing cycles of **InvoMatic**, a study was performed with three different powder mixtures, to show the capacity of the device to provide homogeneous mixtures when compounding with (1) low dosage ingredients, (2) different granulometry ingredients, and (3) multicomponent formulation. All three formulations were mixed through different time (2, 5, and 8 minutes) and speed (10, 50, and 100 RPM) cycles, to verify whether there would be the best working condition for the device. All conditions tested were able to produce homogeneous powder mixtures, with adequate dose uniformity among the compounded capsules even at low mixing time. This shows that **InvoMatic** is suitable and adequate for the day-to-day routine of the compounding pharmacy to produce a broad range of products every day, resulting in fine and homogeneous formulations.

### 4.2 Comparative Tests

After evaluating **InvoMatic** in different working conditions, a comparative test was performed to evaluate the homogenization efficiency between this device and alternative methods (Y-shaped mixer and manual plastic bag technique). All tests were performed under the same mixing condition for each formulation, to validate the comparison. The results showed that the use of **InvoMatic** was superior or at least comparable to the alternative methods, especially when compared to manual mixing, showing that the automation increases the reliability of the mixing process (**Figure 2**). Results present the content uniformity of the single ingredients for formulations (1), (2), and (3).



**Figure 2.** Comparison of the use of InvoMatic with other methods. (1): a) finasteride capsules; (2): b) vitamin B12 and c) folic acid capsules; (3): d) cooper chelate, e) magnesium citrate and f) zinc chelate capsules. AV = Acceptance Value (Ref. USP).

## 5. Applications

**InvoMatic** is a device suitable for the mixing of powders of different granulometry and physical properties and is also suitable for the mixture of liquids and homeopathic formulations. Being compatible with different models of vessels, and with personalizable mixing cycles, liquids of different viscosity can be mixed in the device, in a closed environment, with no risk of cross-contamination.

In homeopathic formulations, especially during globules impregnation, the prescribed solution is added to the inert globules and mixed. This process can be done as a simple impregnation, with the total volume added at once to the formulation, or in triple impregnation, dividing the total volume into three equal additions, followed by a mixing process. In both methods, a controlled time and speed of mixing is needed to ensure the even distribution of the dosage among the globules.<sup>12</sup> **InvoMatic** works in a constant mixing cycle, allowing the solution to be evenly distributed among the globules until complete impregnation, with no left liquid on the bottom of the final formulation that can lead to a lack of uniformity of dosages.



## REFERENCES

1. Ferreira ADO, Brandão MAF, Polonini HC. *Guia Prático Da Farmácia Magistral*. Vol 1.; 2018.
2. Bauman I, Ćurić D, Boban M. Mixing of solids in different mixing devices. *Sadhana - Acad Proc Eng Sci*. 2008;33(6):721-731. doi:10.1007/s12046-008-0030-5
3. Massol-Chaudeur S, Berthiaux H, Dodds JA. Experimental study of the mixing kinetics of binary pharmaceutical powder mixtures in a laboratory hoop mixer. *Chem Eng Sci*. 2002;57(19):4053-4065. doi:10.1016/S0009-2509(02)00262-2
4. Barrett E. The study of pharmaceutical powder mixing through improved flow property characterization and tomographic imaging of blend content uniformity. 2011;(July):367.
5. Asachi M, Nourafkan E, Hassanpour A. A review of current techniques for the evaluation of powder mixing. *Adv Powder Technol*. 2018;29(7):1525-1549. doi:10.1016/j.apt.2018.03.031
6. Deveswaran R, Bharath S, Basavaraj B V, Abraham S, Furtado S, Madhavan V. Concepts and Techniques of Pharmaceutical Powder Mixing Process: A Current Update. *Res J Pharm Technol*. 2009;2(2):245-249.
7. This R, Attribution-noncommercial-noderivs CC, By-nc-nd CC, If T, Rose W. White Rose Research Online URL for this paper: Version: Accepted Version Article: Asachi, M, Nourafkan, E orcid. org / 0000-0002-1898-5528 and Hassanpour, A orcid. org / 0000-0002-7756-1506 ( 2018 ) A review of current techniques for the evaluati. Published online 2018.
8. Bauman I. Solid-solid mixing with static mixers. *Chem Biochem Eng Q*. 2001;15(4):159-165.
9. Lemieux M, Bertrand F, Chaouki J, Gosselin P. Comparative study of the mixing of free-flowing particles in a V-blender and a bin-blender. *Chem Eng Sci*. 2007;62(6):1783-1802. doi:10.1016/j.ces.2006.12.012
10. Dirnböck H, Stachel H. The development of the Oloid. *J Geom Graph*. 1997;1(2):105-118.
11. Kuleshov AS, Hubbard M, Peterson DL, Gede G. Motion of the Oloid-toy. *7<sup>th</sup> Eur Nonlinear Dyn Conf*. 2011;(July):24-29.
12. Bernal GG. How does homoeopathy cure?. A brief history of its causal hypotheses. *Br Homeopath J*. 1995;84(1):40-45. doi:10.1016/S0007-0785(05)80717-3.

**Together**  
we create the future  
of personalizing medicine.



**Fagron BV**  
Lichtenauerlaan 182  
3062 ME Rotterdam  
The Netherlands

T +31 88 33 11 288  
F +31 88 33 11 210  
[www.fagronlab.com](http://www.fagronlab.com)

 **Fagron**  
lab