INTRODUCTION

In modern pharmaceutical compounding, powder blending often consists of geometric addition, a time-consuming process that adds powders incrementally by calculated proportions, and/or the use of expensive equipment, such as a V-blender, to achieve good mixing.

For small to medium volume blends, which could range from approximately 1 mL to 2 L of powders, there is no cost-effective piece of equipment to help the compounder ensure good mixing. As a result, the Inversina Manual Mixer, manufactured by Bioengineering Inc., was evaluated to determine if it could be a time- and cost- effective alternative to geometric addition by hand and/or to expensive, large-volume industrial powder mixers. Furthermore, the mixer was tested for its capabilities concerning liquid-liquid mixing, as this could provide an additional benefit for formulations with differing aqueous phases. The following report delineates the findings of this investigation.

THE MIXING SYSTEM: OLOID TUMBLER

The Inversina Manual Mixer works by rotating a mixing vessel along an oloid geometric pathway (Fig. 1) via a manual rotary handle. The oloid is a cuboid solid which was derived by German mathematician Paul Shatz in 1929, the inclined roll of the 3-dimensional oloid geometry is where the stirring/mixing motion originated from.[1] The mixer comes with two cylindrical mixing vessels made of PET and with volume capacities of 1.5 L and 2.0 L, respectively. The vessel is secured to the mixer with two rubber straps. Additionally, mixing vessels of other dimensions may be used by means of a brush insert that can secure the alternative vessel in the mixer cage (Fig. 2). The mixer may be secured to a table edge via the provided screw C-clamps. The supplier's recommended mode of operation for the mixer is to rotate the handle at a rate of 60 RPM for 3, 5, 10, 15 or 25 minutes for a container volume not exceeding 66% total capacity. [2]

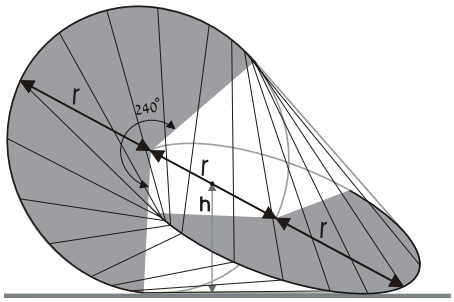

Fig. 1 Oloid geometric pathway

a. Mixer cage
b. Mixing vessel
c. Band clamp
d. Brush insert
e. Laboratory flask

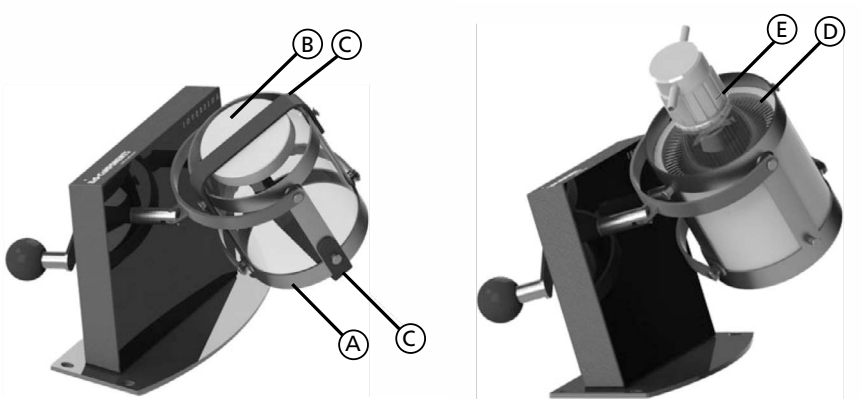

Fig. 2 Inversina Manual Mixer

TESTING

Powder Blending I: Lactose and Dyed Starch in 1.5 L Vessel

Powder Blend 1 consisted of two powders, lactose [Lactose (Monohydrate), NF; NDC: 00315-05; Lot: 28327] and corn starch [Starch, NF (Corn); NDC: 38779-0097-08; Lot: 101143/C], which were mixed in the Inversina 1.5 L PET mixing vessel. Approximately 9 g of starch was first dyed with 2.3 g of red colorant [F.D. & C. Red No. 3 (Powder); NDC: 38779-1278-4; Lot: AL1569/A] and then placed with 60 g of lactose in the mixing vessel, as shown in Fig. 3.

The 1.5 L vessel was secured to the mixer and rotated steadily by hand (~60 RPM). The powder blend was observed at four time intervals (10 s, 30 s, 45 s and 60 s) during the mixing process and then analyzed with a microscope [National DC5-163 Digital Microscope DMB2-223, 29AX E250223, Serial No. 31304719] to discern homogeneity at a micro level.

Fig. 3 (left) Lactose and dyed starch, (right) lactose and dyed starch in 1.5 L PET vessel before mixing

Powder Blending II: Methylcellulose and Colorant in Various Unguator Jars

Powder blends of methylcellulose [Methycellulose (USP), NDC: 0085-05; Lot: 47796/B] and colorant [F.D. & C. Red No. 3 (Powder); NDC: 38779-1278-4; Lot: AL1569/A] were tested with the mixer in varying proportions and mixing vessels, as shown in Table 1 and Fig. 4.

Table 1. Proportions of for methylcellulose to colorant for powder blends

	Weight of Methylcellulose	Weight of Colorant	Mixing Vessel
Powder Blend 2	3.0 g	0.10 g	20 mL Unguator jar
Powder Blend 3	10.0 g	0.25 g	50 mL Unguator jar
Powder Blend 4	20.0 g	0.50 g	100 mL Unguator jar

Fig. 4 Methylcellulose and colorant for powder blends in various Unguator jars before mixing

The Unguator jars were secured in the Inversina using the brush insert, as demonstrated in Fig. 5. Each vessel was rotated steadily by hand and the powder blends were observed at four time intervals (10 s, 30 s, 45 s and 60 s) during the mixing process, respectively, and then analyzed with the microscope to discern homogeneity at a micro level.

Fig. 5 100 mL Unguator jar secured by brush insert in Inversina Manual Mixer

Liquid Mixing: Ursodiol in Oral Blend in 1.5 L and 2.0 L Vessels

In order to test the liquid mixing capabilities of the Inversina, common oral formulations consisting of ursodiol [Ursodiol (USP); NDC: 1987-04; Lot: 66272/C], glycerin [Glycerin (USP); NDC: 0613-08; 44739/B], oral syrup [Oral Syrup; NDC: 2511-08; Lot: 1073/A] and oral suspend [Oral Suspend; NDC: 2510-08; Lot: 1072/A] were tested. The formulas may be found in Table 2 below.

Table 2. Oral Blend Formulations

	Volume of oral syrup	Volume of oral suspend	Volume of glycerin	Weight of ursodiol	Mixing Vessel
Aqueous Blend 1	50 mL	50 mL	5.0 mL	2.5 g	1.5 L PET jar
Aqueous Blend 2	100 mL	100 mL	10.0 mL	5.0 g	2.0 L PET jar

The ursodiol was first levigated with glycerin to produce a white, thick paste. This was then placed in the mixing vessel along with the oral syrup and oral suspend. The aqueous phases were visibly separated, as shown in Fig. 6.

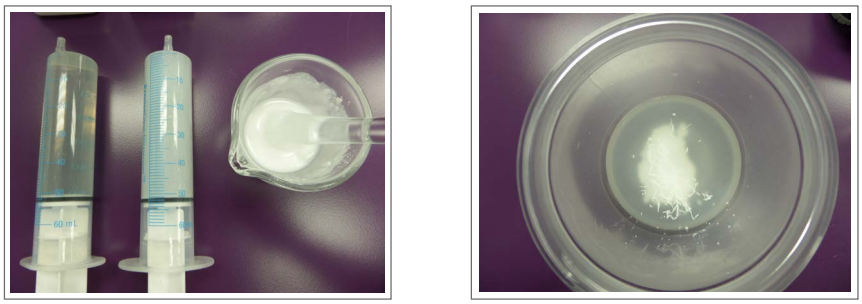

Fig. 6 (left) Oral syrup, oral suspend and levigated ursodiol, (right) liquid blend in 1.5 L PET mixing vessel

The aqueous materials were mixed with the Inversina by rotating the manual handle continuously and steadily. The liquid blends were observed at four time intervals (10 s, 30 s, 45 s and 60 s) during the mixing process, respectively.

Percent Loss of Powder in Container

This test was performed to see what amounts of powders were lost in transfer while using an Inversina mixer. Progesterone, which is a very sticky and static powder, was used with two different excipients (CapsuBlend®-P and Lactose). One additional test was performed using standard Sodium Chloride.

The capsule formulation done was for 50 capsules of #0 with a capsule volume of 0.68 mL. The mixing performed on the Inversina was done at a rate of 60 RPM for 1 minute.

Table 3. Quantities of Powders

Test	Ingredient	Qty.	Total
1	Progesterone (micronized), USP	10 g	20.669 g
	CapsuBlend®-P	10.669 g	
2	Progesterone (micronized), USP	10 g	18.226 g
	Lactose	8.226 g	
3	Sodium Chloride	43.146 g	43.146 g

RESULTS AND OBSERVATIONS

Powder Blending I: Lactose and Dyed Starch in 1.5 L Vessel

Powder Blend 1 was found to be well mixed at 30 seconds, as shown in Fig. 7. Agglomerations occurred during mixing as no shear forces were created; however, a homogenous powder blend is achievable, as denoted by the microscope photo in Fig. 8.

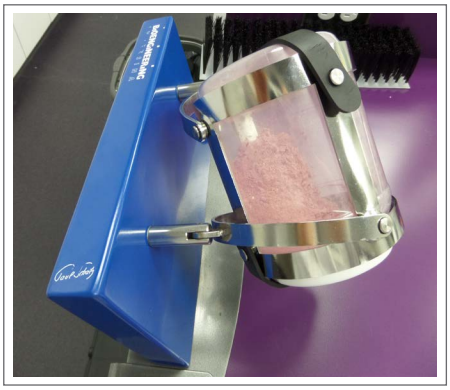

Fig. 7 Powder Blend 1 at 30 seconds

Fig. 8 Microscope view of Powder Blend 1 at 60 seconds (40x magnitude)

Powder Blending II: Methylcellulose and Colorant in Various Unguator Jars

Results similar to Powder Blend 1 were found for Powder Blends 2, 3 and 4. Generally, good mixing could be achieved at 30 seconds and a homogenous powder blend was obtained at 60 seconds. Figs. 9, 11, and 13 depict the powder blends at the four different time intervals during the mixing process. Figs. 10, 12 and 14 are the microscopic views of each blend at 60 seconds.

Fig. 9 Powder Blend 2 at 10 s, 30 s, 45 s and 60 s, respectively

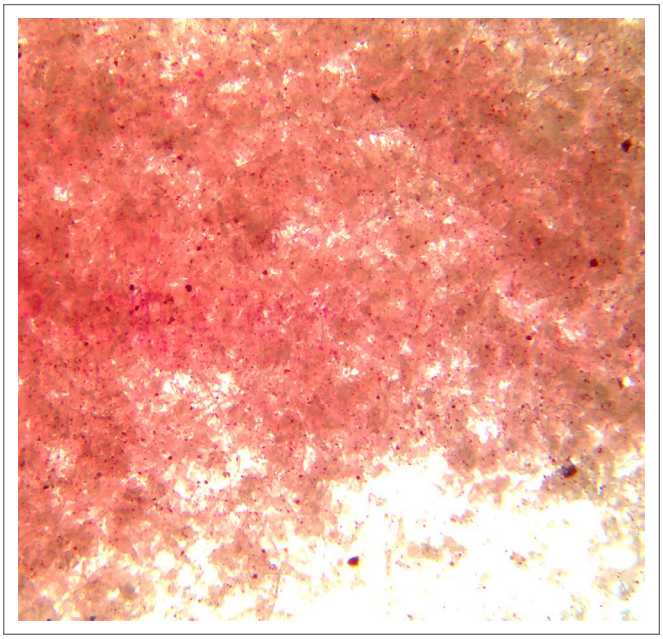

Fig. 10 Microscope view of Powder Blend 2 at 60 seconds (40x magnitude)

Powder Blending II: Methylcellulose and Colorant in Various Unguator Jars (Continued)

Fig.11 Powder Blend 3 at 10 s, 30 s, 45 s and 60 s, respectively

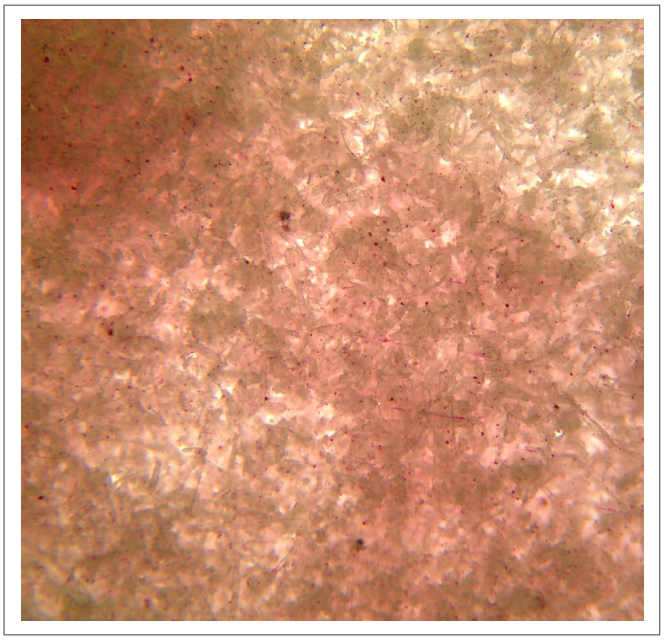

Fig. 12 Microscope view of Powder Blend 3 at 60 seconds (40x magnitude)

Fig. 13 Powder Blend 4 at 10 s, 30 s, 45 s and 60 s, respectively

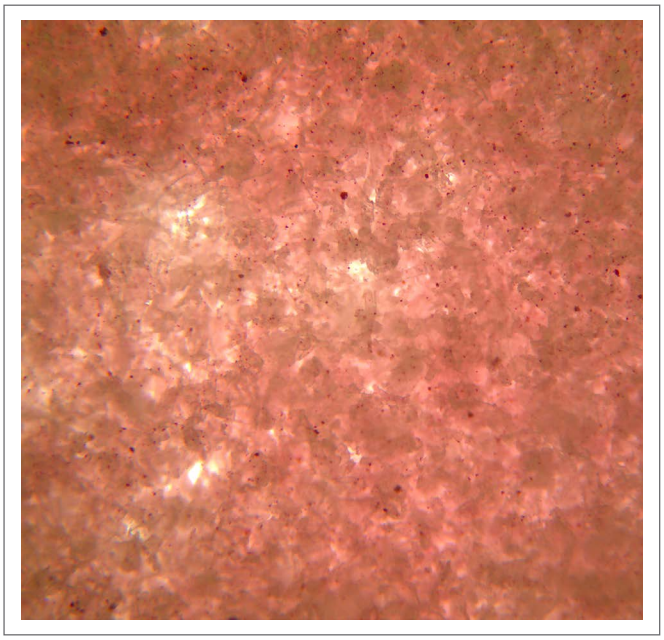

Fig. 14 Microscope view of Powder Blend 4 at 60 seconds (40x magnitude)

Liquid Mixing: Ursodiol in Oral Blend in 1.5 L and 2.0 L Vessels

Qualitatively, a stable, homogeneous aqueous mixture was achievable at 60 seconds for both liquid blends. Fig. 15 shows the homogenous oral formulations at 60 seconds of the mixing process.

Fig. 15 (left) Liquid Blend 1 at 60 seconds, (right) Liquid Blend 2 at 60 seconds

Percent Loss of Powder in PET Container

A powder blend for a 200 mg Progesterone capsule formulation (50 capsules) was mixed in the Inversina mixer to assess powder loss when a static-prone powder is mixed in a PET container with an appropriate excipient blend. Powder loss was minimal at 0.68%.

Progesterone (10.0 g) + CapsuBlend®-P (10.7 g) → **0.68%** loss in container.

CONCLUSION

The Inversina Manual Mixer provides a cost-effective and time-saving option to a compounding pharmacist seeking to mix powders or liquids using proven mixing technology (Oloid motion). Testing has shown that a visibly homogenous powder mixture can be achieved by mixing for 1-2 minutes at 60 RPM. Further tests with Progesterone demonstrate that static-prone powders can also be effectively mixed in the Inversina PET container with minimal powder loss.

It should be noted that as there is no shear force provided by this system of mixing, it will not reduce particle size and cannot replace the trituration process.

REFERENCES

[1] Paul Schatz Biography Website, "Paul Schatz Stiftung: The Oloid," http://www.paul-schatz.ch/en/discoveries/the-oloid/ (current July 7th, 2015)

[2] BioComponents website, "Inversina Frequently Asked Questions", http://www.inversina.com/main/faq, (Current July 9th, 2015)