Prescription Compounding in UnoDose® Metered-Dose Topical Applicators using an Electronic Mortar and Pestle

Synopsis

Mixing directly in UnoDose® topical applicators using the Reflex Medical mixing paddle is a simple, convenient way to compound topical hormone replacement prescriptions. We investigated the parameters used on an electronic mortar and pestle machine that can achieve homogeneous mixtures for these formulations. We tested multiple combinations of mixing speed and mixing time using different creams and API substitutes. This white paper presents those results, which offer insight into appropriate mixing speeds and times. Compounding pharmacies can refer to these results and recommendations when defining standardized procedures.

Introduction

The UnoDose® metered-dose topical applicator allows pharmacies to mix compounded topical prescriptions right in the applicator. This improves productivity and technique, and reduces costs by:

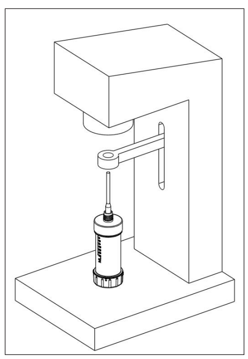
- Minimizing waste of cream and drug
- Eliminating jar-to-applicator transfer steps
- Reducing clean-up steps
- Decreasing technician drug exposure

For mechanically mixed topical creams, the following properties must be considered when defining compounding parameters:

- Homogeneity of active pharmaceutical ingredients (API) in the final mixture
- Specific gravity of the mixed cream
- Characteristics of the APIs, additives, and carrier creams

In this white paper, we report test results for mixing in UnoDose applicators, and offer recommendations that can help when defining compounding procedures for hormone replacement therapy (HRT) preparations.

Electronic Mortar and Pestle Machines

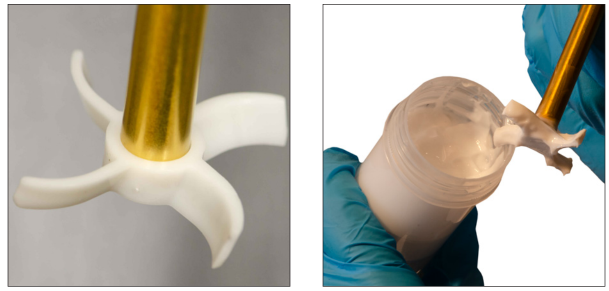

Electronic mortar and pestle machine

These machines are commonly used to mix an API with a carrier cream to create topical prescriptions for UnoDose applicators. They have a movable "lift" arm that accepts the UnoDose, and a separate mixing blade attached to a rotating shaft. The arm moves up and down at the same time that the blade rotates, which together agitate the cream and API into a homogeneous mixture.

Two parameters control the mixing process: rotational speed (rpms) and time. Vigorously agitating any liquid or cream whips air into the mixture, which is called air entrapment. The higher the rpms and the longer the mix time, the more air is entrapped. The consequences are reducing the specific gravity, decreasing the potency by volume, and increasing the variability of the mixture.

UnoDose Mixing Paddles

The UnoDose mixing paddle*, produced by Reflex Medical for use with UnoDose applicators, was used for all testing for this white paper, so results and recommendations only apply to it. The paddle has a unique vane


UnoDose mixing paddle

design, which pushes cream downward and air upward to rapidly achieve a homogeneous mixture while minimizing air entrapment. The paddle is designed to easily remove any residual cream, and is disposable, obviating the need to clean it for reuse.

The vanes contact the bottom, top (i.e. mixing lid), and inside of the UnoDose container so there are no stagnant areas for API to pool. Although the vanes contact the inner wall of the container, any grinding or de-clumping effects are unlikely to be reliable in large mix volumes.

Basics of Compounding with Creams

Specific Gravity

Topical creams are emulsions with a specific gravity close to, but not the same as, water. Published values for different creams range from 0.8 to 1.1. (In gram and milliliter units, density and specific gravity are equal, where 1 gram/milliliter is a specific gravity of 1.) Some vary more than +/-10% according to manufacturers' specifications. Moreover, creams become less dense with mechanical mixing due to air entrapment. In some cases, this can be a 10% reduction or more.

The consequences of a deviation in specific gravity are twofold, affecting:

1. the drug potency per milliliter of compounded mixture, and
2. the weight of cream required for the desired final volume.

UnoDose applicators, like all metered-dose devices, dispense by volume not weight. If a mixed cream has a specific gravity of 0.9, the potency per milliliter is 90% of the potency per gram, and patients get the drug amount based on volume, not weight. This may not be significant in HRT because patients are titrated to effect. Nonetheless, it is good practice to avoid entrapping air as much as possible, and to standardize protocols for consistent potency.

Variations in specific gravity can be significant for a pharmacy's procedures. For example, the recommended fill volume to provide 30 useable milliliters is 33 milliliters.

* US Patent D891,634. Other patents pending.

But if the final specific gravity is 0.9, weighing out 33 grams for the mix gives 36.7 milliliters, or almost four milliliters more than required. Pharmacies should take this into account when defining standard procedures.

Homogeneity

Achieving homogeneity when compounding with electronic mortar and pestle machines requires selecting a suitable combination of time and rotational speed that will uniformly distribute the API throughout the container. Nonetheless, large particles or clumps, even if equally distributed, would not be satisfactory. To assure homogeneity at a micro level, carrier creams, diluents, excipients, and API formulations (e.g. micronized) must be carefully selected. Moreover, geometric dilution, trituration, and levigation steps should be included as needed.

Performance Evaluation

Scope

Because the possible combinations of APIs, creams or gels, and compounding techniques is unlimited, our testing focused on some of the most common components and combinations using only the Reflex mixing paddle. The outcome using anything outside these parameters, such as highly viscous creams and ointments or gels cannot be assumed from the results of this study. The parameters and characteristics we tested are:

- Mixing time—1 to 4 minutes based on typical usage.
- Mixing speed (rpms)—Based on experience, high rpms do little to reduce time to homogeneity while increasing air entrapment, so our studies were limited to 300, 600, and 1000 rpms.
- API load—HRT drug concentrations range from 0.1% or less to 20% or more, but two groups stand out: a lower of 0.1–2%, and a higher of 5–20%. We used 0.5% and 10% of our API substitutes.
- API composition—HRT drugs are suppled as powders, but may be reconstituted prior to compounding. We investigated both liquid and powder API substitutes.
- Viscosity—We evaluated creams with three different average viscosities: 60,000 centipoise (cp) (HRT Botanical™), 175,000 cp (HRT Supreme), and 475,000 cp (VersaPro™ cream).
- Value of simethicone as an anti-foaming agent.

Assumptions

Foremost in our assumptions for evaluating homogeneity is that an API or API preparation is fully and readily soluble in the selected carrier. This study evaluates distribution of APIs with mechanical mixing. API dissolution and micro-level homogeneity are separate issues.

The gold standard for potency testing in compounding is high performance liquid chromatography analysis (HPLC) of API concentration. But the cost of using HPLC to examine multiple variables would be excessive. Our goal was to recommend mixing parameters for best results and efficiencies, which can be studied with other methods. We performed our homogeneity tests using dye as an API substitute, and a precision colorimeter as a measurement instrument. Using individualized calibration curves, this appears to be a robust indicator of dye concentration. Moreover, the colorimeter method captures volume-based potency variations inaccessible to HPLC.

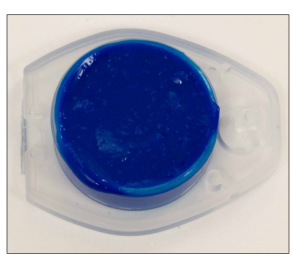
Because we used substitute API in this study, potency cannot be directly confirmed. Nonetheless, accurate weight-based potency can be assumed as long as the final mixture is homogenous, and proper pharmacy technique has been employed (weighing ingredients, preparing APIs, selecting components).

We expected viscosity to be important when selecting mixing parameters. Many creams and gels are not pourable or self-leveling, but act like solids unless vigorously agitated. Their viscosity is not a fixed value, but depends on the intensity of agitation (i.e. thixotropic). Manufacturers' specifications show up to a tenfold difference among creams used in HRT compounding, and the effect this has on mixing results was uncertain. We started with the assumption that similar viscosity creams behave similarly.

Homogeneity Test Method

To test for homogeneity, we used a Konica Minolta CR-300 Chroma Meter colorimeter to measure the color of 1 milliliter aliquots of cream. Standardized loads of blue FD&C food coloring were added to all mixes. After mixing, the aliquots were dispensed from the UnoDose applicator and loaded in order into miniature cuvettes. Colorimeter readings were output as CIE L*a*b* values.

Calibration standards in a range of +/-20 percent around the standardized concentrations were used to



Loaded cuvette

Colorimeter setup

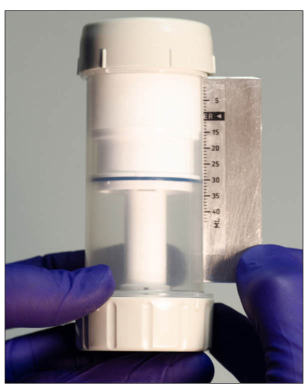
create calibration curves for each cream. We statistically analyzed the repeatability of colorimeter readings and found a reading-to-reading standard deviation of better than 0.2% for the same aliquot, and a sample-to-sample standard deviation of better than 2% for the same calibration mix. These suggest adequate repeatability and sensitivity for the method.

For 0.5% mixtures, approximately 150 milligrams of dye was used, either directly as a powder or dissolved in 1.2 grams of water solution. This was added to the cream for 30 grams total (i.e. 5 mg/gm). For 10% mixes, 150 milligrams of dye were premixed with 2.85 grams of lactose powder. This was used directly for powder mixes, or levigated in 1.5 grams of ethoxydiglycol for liquid mixes, then added to a total of 30 grams (i.e. 3 grams in 30, or 100 mg/gm). Correction factors, based on actual weights of mix constituents, were applied to all calculations.

We compared aliquots from a single mix to each other, rather than between mixes. Thus, the method is insensitive to small variations in average dye concentration or procedure, and provides a powerful measure of dye dispersion within any one mix.

Specific Gravity Test Method

To measure specific gravity, we used the UnoDose container as a graduated cylinder, being sure to remove all air. This method avoids any errors from transferring to another vessel. The volumetric accuracy of the UnoDose has been extensively validated, and manufacturing tolerances are tightly controlled. By using a specially calibrated volume scale, and UnoDose containers as the reference, an accurate comparison between mixed and unmixed samples is possible, which is reported as a percent change.



Calibrated volume scale

Results: Homogeneity

The figures and tables below are results of homogeneity testing from some of the parameter combinations. They show normalized % dye vs. collected sample number, first to last, along with a trend line for each set. Figure 1 shows how the data were evaluated. Important characteristics to note are: 1) the linear trend, and 2) the variability as quantified by standard deviation about the mean. In subsequent figures, the points have been omitted for clarity, but the distribution of Figure 1 typifies other figures.

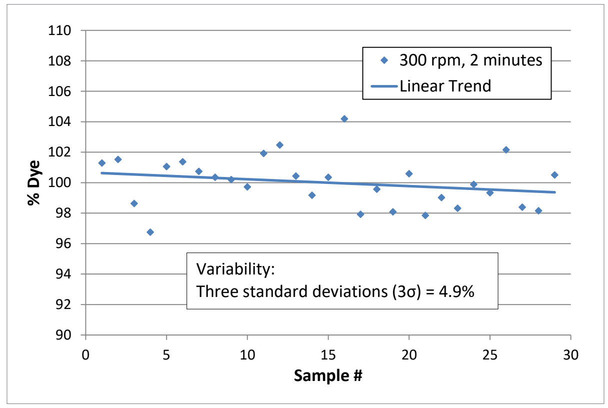


Figure 1. 300 rpm mix for 2 minutes for 0.5% liquid dye in cream with an average viscosity of 175,000 cp.

All data were normalized to a mean of 100%. In other words, a mix's average reading is assumed to be 100%, and variations are relative to that. This allows direct comparison of homogeneity results from mix to mix.

The linear trend line characterizes distribution of dye in dispensed doses, whereas the standard deviation characterizes overall variability of readings. Although a sloped trend line directly affects standard deviation, high variability could exist even if the trend line is flat. So although a flat trend line is ideal, it must be accompanied by an acceptably low variability to confirm homogeneity.

Homogeneity vs. Time and Mixing Speed for Medium Cream

Figure 2 shows how the linear trend varies with mixing time at one mixing speed for a typical medium viscosity cream. Table 1 shows the variability for those combinations as well as variability for some other mixing speeds. The 1 minute results suggest incomplete mixing for this combination. The higher variability for 1000 rpm sug-

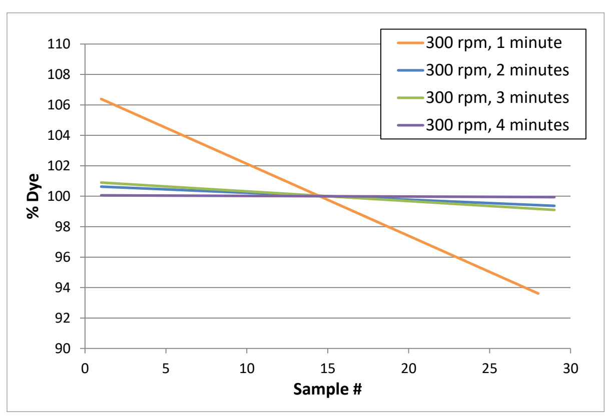


Figure 2. Linear trend of 300 rpm mixes for 1, 2, 3, and 4 minutes for cream with an average viscosity of 175,000 cp and 0.5% liquid dye.

	Mixing Time (minutes)			
rpm	1:00	2:00	3:00	4:00
300	±13.0%	±4.9%	±4.2%	±4.2%
600	±5.0%	±4.1%	±3.8%	
1000	±7.3%	±7.0%		

Table 1. Three relative standard deviations (3σ) of % dye concentration for cream with an average viscosity of 175,000 cp.

gests that higher speed does little to enhance mixing. Although not shown on Figure 2, the related linear trends confirm this as well, ranging from about 97% to 103%. For all combinations of 300 and 600 rpm and 2, 3, or 4 minutes, variabilities and linear trends are comparable. All have linear trends within ±1% and 3σ variability less than 5%.

Homogeneity vs. Time and Mixing Speed for Thin Cream

Figure 3 and Table 2 for a thin cream show that homogeneity is reached by 2 minutes at 300 rpm, and that further mixing offers little improvement. In this case, 1 minute at 600 rpm might yield homogeneity, but this combination does not yield homogeneity with other creams.

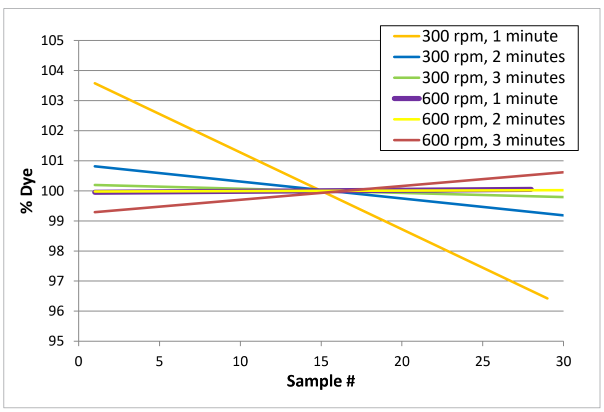


Figure 3. Linear trends for 300 and 600 rpm mixes with 0.5% liquid dye for 1, 2, and 3 minutes for cream with an average viscosity of 60,000 cp.

	Time (minutes)		
Speed (rpm)	1:00	2:00	3:00
300	±17.0	±5.3	±3.6
600	±4.9	±7.0	±6.0

Table 2. Three relative standard deviations (3σ) of % dye concentration for cream with a viscosity of 60,000 cp.

Homogeneity vs. Time and Mixing Speed for Thick Cream

The linear trends in Figure 4 show that 2 minute mixes at any speed yield similar results, and that 1 minute is inadequate for achieving homogeneity with this thicker cream and API substitute. Table 3 confirms that, but also shows a wider variability for this cream than with thinner creams.

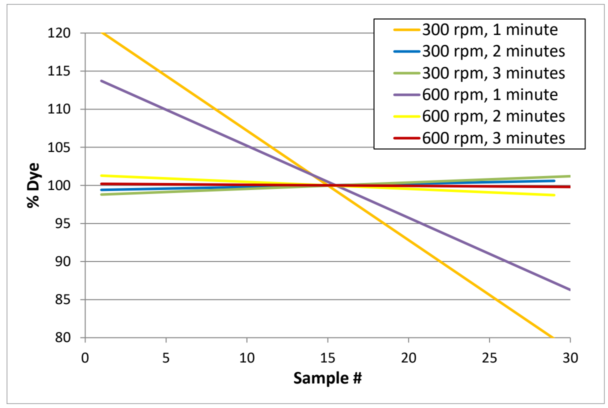


Figure 4. 300 and 600 rpm mixes with 0.5% liquid dye for 1, 2, and 3 minutes for cream with an average viscosity of 475,000 cp.

	Time (minutes)		
Speed (rpm)	1:00	2:00	3:00
300	±41.0	±6.5	±9.1
600	±32.9	±8.3	±7.1

Table 3. Three relative standard deviations (3σ) of % dye concentration for cream with a viscosity of 475,000 cp.

Homogeneity vs. API Type

Figure 5 shows that the form of the API—liquid, powder, low strength, high strength—has little effect on how well the mixing process distributes an API.

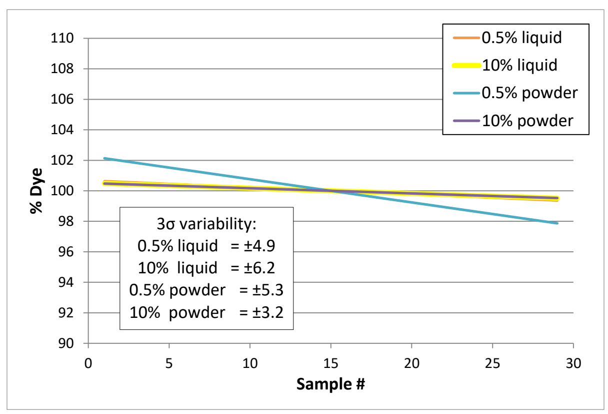


Figure 5. Linear trend and variability comparison of API types mixed at 300 rpm for 2 minutes for cream with an average viscosity of 175,000 cp.

Homogeneity vs. Viscosity Comparison for Like Parameters

The trend lines of Figure 6 show that the high viscosity cream is slightly more difficult to disperse the API than thinner creams. The difference is unlikely to be significant, although the variability is higher.

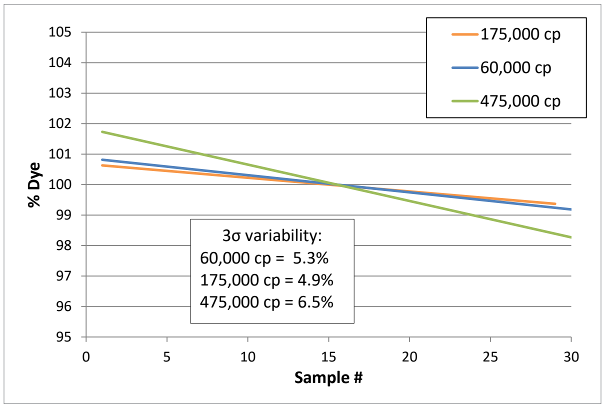


Figure 6. Linear trend and variability comparison of three different viscosity creams mixed at 300 rpm for 2 minutes.

Homogeneity vs. API placement

Figure 7 compares differences in homogeneity obtained when the initial API location is higher or lower in the UnoDose applicator. Neither the very bottom nor the very top are recommended API locations when mixing, so these were not included.

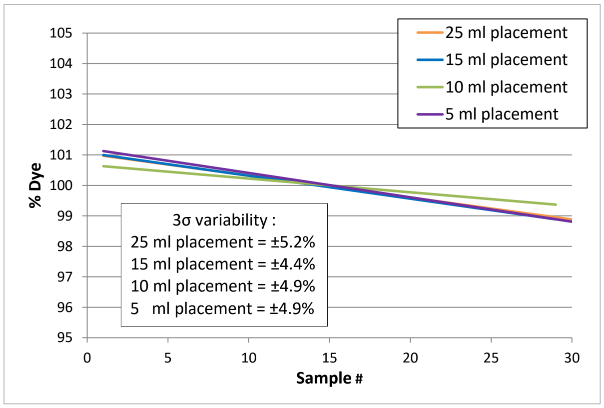


Figure 7. Linear trend of homogeneity for various placements of API substitute for cream with an average viscosity of 175,000 cp and 0.5% liquid dye, mixed at 300 rpm for 2 minutes.

Results: Specific Gravity

Tables 4 through 8 show the % change in specific gravity after mixing for some combinations of time and speed for different viscosities and conditions.

Time and Speed vs. Viscosity

	Time (minutes)	
Mixing Speed (rpm)	2:00	3:00
300	-1.3	-2.0
600	-2.8	-4.9
1000	-6.9	-8.0

Table 4. Percent change in specific gravity after mixing a cream with a viscosity of 175,000 cp. Measured specific gravity of unmixed cream = 1.00. Air was removed during the filling procedure.

	Time (minutes)	
Mixing Speed (rpm)	2:00	3:00
300	-6.2	-10.1
600	-7.6	-12.1
1000	-6.4	-10.5

Table 5. Percent change in specific gravity after mixing a cream with a viscosity of 60,000 cp. Measured specific gravity of unmixed cream = 1.01. This cream is self-leveling, so no air is in the pre-mix load.

	Time (minutes)	
Mixing Speed (rpm)	2:00	3:00
300	-6.3	-7.4
600	-8.2	-12.3
1000	-13.8	-19.1

Table 6. Percent change in specific gravity after mixing a cream with a viscosity of 475,000 cp. Measured specific gravity of unmixed cream = 0.99. Air was removed during the filling procedure.

Pre-Mix Loading Method

	Time 2:00		Time 3:00	
Viscosity	yes	no	yes	no
175,000 cp	-1.3	-1.7	-2.0	-1.1
475,000 cp	-6.3	-7.0	-7.4	-8.8

Table 7. Comparison of removing or not removing air while loading the UnoDose prior to mixing at 300 rpm, showing percent change of specific gravity after mixing.

Simethicone Additive

		Time 2:00		Time 3:00	
Viscosity	Speed (rpm)	yes	no	yes	no
175,000 cp	300	-1.3	-1.7	-2.0	-1.1
	600	-2.8	-4.1	-4.9	-3.2
475,000 cp	300	-6.3	-6.2	-7.4	-8.6
	600	-8.2	-5.3	-12.3	-8.0
60,000 cp	300	-6.2	-5.3	-10.1	-7.2
	600	-7.6	-7.0	-12.1	-9.1

Table 8. Comparison of mixing with and without a 2% addition of simethicone in cream, showing percent change of specific gravity after mixing.

Discussion

In the homogeneity figures, Sample #s are displayed in the order dispensed, but this is not exactly the top-to-bottom distribution. Cream does not move upward as a "plug," and separate flow studies have shown slight mixing of lower levels with upper levels during dispensing. This does not negate the validity of this data since it represents actual use.

Air entrapment directly affects the dye concentration as read by the colorimeter. Our methods are sensitive to this real variation, whereas weight-based measurements like HPLC are not. These data were not intended to confirm potency, but specific gravity results offer insight into potency on a volume basis.

The linear trend appears to be the best indicator of adequate API dispersion. Once that line approaches flat, further mixing does little, if anything, to improve the variability. In some cases, variability actually increased with longer mixing times. This is likely due to entrapping more air, which could increase variability.

Although the variability for some mixes with flat linear trends is slightly above 5%, note that these are 3σ values. Moreover, this variability includes inaccuracies attributed to the method. Considering that acceptable compounding potencies of +/-10% are widely cited, a flat linear trend confirms good results.

Higher mixing speeds appear to offer no benefit for dispersing the API or minimizing variability. In some cases, variability actually increased with higher speed. The likely explanation is that vertical paddle excursions, not rotation, distribute the API from top to bottom, which are controlled by time only. For thin cream, obtaining homogeneity with higher speed (600 rpm) for a shorter time (1 minute) might work, but we generally found mixing for only 1 minute unreliable.

What effect higher mixing speeds and longer times might have on micro-level homogeneity was not part of this investigation, and either or both might facilitate API dissolution if that is a concern. Also, note that these data apply only to the UnoDose mixing paddle. Performance of other blades was not evaluated for this study.

Air entrapment, and the corresponding decrease in specific gravity, is an important consideration. Higher speeds clearly increase air entrapment without an advantageous decrease in mixing time required for API dispersion. This is especially true for thick cream with a low specific gravity to start with, where we saw specific gravities below 0.8 for some mixing parameters.

Taking into account homogeneity and air entrapment results together, mixing at the slowest speed (300 rpm) for long enough to obtain adequate API dispersion is the best combination. The data suggest a mixing time of 2 minutes is adequate for most situations. Longer times may improve dispersion, but can increase both air entrapment and a related variability.

Because mixing parameters significantly affect the final specific gravity, standardized procedures should be adopted to assure repeatable volumetric potency of prescriptions.

Thinner creams mix easier than thicker ones, but viscosity alone isn't the only governing attribute. Solubility and miscibility play roles in obtaining homogeneity at the micro level. We believe the variability we saw with some cream and dye combinations was due in part to incomplete mixing of component phases rather than incomplete dispersion (Table 3 and Figure 4). This underscores the importance of matching cream, API, and excipient for solubility.

The propensity to entrap air may also play a role in both homogeneity and specific gravity results. For example, the medium viscosity cream actually entrapped less air than either the thinner or thicker one (Tables 4, 5, and 6).

Simethicone did little to reduce air entrapment, with the possible exception of higher speeds for longer times, which is probably unnecessary. The purported use of simethicone is anti-foaming, but the air entrapment exhibited in this mixing is likely not analogous to foaming.

Although the API starting location has little effect on achieving homogeneity, it is important to avoid the very top, or, especially, the very bottom. A layer of cream should cover the bottom of the applicator before API is added. Observations suggest that mixing upward is easier than downward, so adding 5 to 15 grams of cream first is recommended.

Although applicators must be primed after mixing to remove all air, data show that removing air during pre-mix filling is unnecessary with the Reflex mixing paddle. Nonetheless, some "tapping" may still be required to cover the bottom before mixing, and to flatten the top of the cream afterward.

Key Findings and Recommendations

- High mixing speeds do little to speed up API distribution, while increasing air entrapment.
- Low mixing speeds minimize air entrapment, and will produce homogeneous mixes.
- Mixing at the slowest speed (300 rpm) for 2 to 3 minutes is adequate for most situations. Times less than 2 minutes are generally unreliable.
- Thin creams mix easier than thick, but the difference for most HRT preparations is minor.
- Once the API is dispersed, further mixing does not improve homogeneity, and can increase variability.
- Standardize compounding procedures and mixing parameters for repeatable volumetric potency.
- Cover the UnoDose bottom fully with cream before adding APIs or solvents, then add cream above them. They should reside neither at the bottom nor the top before mixing.
- Removing air during pre-mix filling is unnecessary when using the Reflex mixing paddle.
- Simethicone does not reduce air entrapment in typical HRT preparations.
- Solubility and miscibility play major roles in obtaining micro-level homogeneity. Choose solvents, excipients, and APIs to optimize dissolution in the compounding vehicle.
- Prepare APIs with trituration, levigation, and geometric dilution as required.

uno DOSE® Metered-Dose Topical Applicator

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