Topical Metered-dosing Dispenser Performance Evaluation

Qiang Liu, PhD
Thomas C. Kupiec, PhD
Nicole T. Vu, PhD

ACKNOWLEDGMENT

This study was supported in part through a grant from DoseLogix.

ABSTRACT

Topical metered-dosing dispensers are designed for dosing accuracy and ease-of-use by the patients while protecting the packaged products from environmental exposure and contamination. The objective of this study was to evaluate the accuracy, precision, and residual of available topical metered–dosing dispensers with different types of topical cream for practical application. Triplicate samples of five different dispensers were tested. This test was completed using three types of commercial topical cream-bases of dissimilar Total Active Pharmaceutical Ingredient Load Percentages, Transdermal Penetration Percentages, and Specific Gravities. The dispensers were evaluated according to specified dose-uniformity criteria for a total dispensing capacity of 30 mL at 0.5 mL per dose for 60 doses. The study shows Topi-CLICK performed with the best precision and accuracy of dosing in comparison to the airless-pump type dispensers. While the dispensing was highly variable with airless pumps and may require calibration for each packaged product, remarkably the performance of Topi-CLICK was not affected by different types of cream-bases and does not require additional metering calibration.

INTRODUCTION

The worldwide market for prescription dermatological drugs exceeded 21 billion dollars in 2015. A recent press release by the market research firm Kalorama Information revealed that the dermatology field grew at a rate of 7.9% from 2013 to 2015, with the psoriasis and skin cancer treatments showing significant increase in the last two years.[1] In fact, about 25% of total healthcare spending is for dermatological conditions that require topical therapies such as acne, dermatitis, hair loss, psoriasis, skin cancer, seborrhea, and infection.[1-2] Not included in this record is an ever-expanding market of emollients, skin cleansers, sunscreens, hormone replacement, and topical pain medications.[2] The growth and aging of the world population and the availability of new products and technologies are the driving forces in this busy market.[1]

Topical therapies are usually self-administered by the patient. For this reason, treatment regimen and dispensing that complement a patient's activity and capability will enhance patient compliance rates.[3,4] Topical delivery systems that incorporate child-resistance features with intuitive designs can offer easy access to medication with safe use and can add value to the drug product.[2] Compared to traditional bottles, tubes, or jars, metered-dosing dispensers can be engineered and customized to different user groups or preferences.[2-3] More than 90% of topical medications are in the form of lotions, creams, ointments, gels, pastes, or foams.[2] Administering an accurate dose of these topical dosage forms is a challenge because the quantity of drug dispensed per application may be affected by the type of cream and the type of dispenser used. Inaccurate dosing of a product will not produce optimal results within a treatment period and may increase risk of irritation or other side effects. Consequently, this raises the overall costs of therapy.[4]

Knowing the amount of drug dispensed per application is important both to optimize treatment and to estimate the total number of applicable doses, as well as the duration of use for the required product label.[4] This paper presents data from a study that evaluated the accuracy, precision, and residual of five commercially available metered–dosing dispensers during simulated in-use testing using three types of commercial topical cream-bases. Included in this study were five metered-dosing dispensers: four commercially available airless pumps and a dial-click syringe with an applicator (Topi-CLICK).[5] The major difference among these metered-dosing dispensers is the mechanisms for dispensing and metering. Other variations include the number of actuations required to dispense a 0.5-mL dose and one of the metered-dosing dispensers having an applicator upon which the topical dose is dispensed.

SIMULATED IN-USE TESTING FOR UNIFORMITY OF DOSE

The five metered-dosing dispensers analyzed are identified in Table 1. Metered-dosing dispenser A is a dial-click syringe (Topi-CLICK); metered-dosing dispensers B and C are airless pumps with collapsible pouches, and metered-dosing dispensers D and E are airless pumps with pistons. Both metered-dosing dispensers A and B were designed to deliver 0.25 mL of product with each actuation, while each actuation of the C, D, and E airless pumps was intended for

The authors are affiliated with Analytical Research Laboratories, Inc., Oklahoma City, Oklahoma.

0.5-mL dosing. The metered-dosing dispensers were selected to have equal 30-mL label capacity or 60 doses at 0.5 mL per dose. To determine the uniformity of the dispensed amounts throughout the life of each metered-dosing dispenser unit, the accuracy and consistency in dispensing the target dose of 0.5 mL were assessed for a total of 60 doses, or until no further cream-base could be dispensed with actuation using three different commercially available cream-bases for test media. These three readily available cream-bases are typical cream-bases used in compounding of topical preparations. To represent the variations in cream-bases used in compounding, these three cream-bases were selected having dissimilar Total Active Pharmaceutical Ingredient Load Percentages, Transdermal Penetration Percentages, and Specific Gravities. Properties of the cream-bases used in this study are listed in Table 2 and can be accessed at the manufacturer's website listed in the references.[6-8]

TABLE 1. Design Variations of the Five Tested Topical Metered-dosing Dispensers.

DISPENSER	DISPENSER MECHANISM	LABEL QUANTITY OF DISPENSES AT 0.5 ML PER DOSE	PUBLISHED DISPENSE VOLUME(ML/ ACTUATION)
Dispenser A (Topi-CLICK)	Dial-click syringe with applicator	60	0.25
Dispenser B	Airless pump with collapsible pouch	60	0.25
Dispenser C	Airless pump with collapsible pouch	60	0.5
Dispenser D	Airless pump with piston	60	0.5
Dispenser E	Airless pump with piston	60	0.5

TABLE 2. Properties of the Cream-bases.[5-7]

CREAM-BASE IDENTIFIER	SPECIFIC GRAVITY (TO WATER)	TOTAL API LOAD	TRANSDERMAL PENETRATION
Thin	1	35%	80%
Medium	0.96	30%	70%
Thick	0.9	20%	40%

API - active pharmaceutical ingredient

PREPARATION OF THE DISPENSERS

The entire experiment was conducted by one operator. The weights of empty metered-dosing dispenser assemblies without their protective caps were recorded (Table 7). Then, each unit was completely filled with cream-base. During the filling process, the metered-dosing dispensers were tapped every one third of the total unit's volume to remove air bubbles. The filled units were weighed before and after priming (Table 4). Each metered-dosing dispenser was primed by actuating until approximately 30 mL of cream-base remained in the metered-dosing dispenser. The net volume for each test unit was then calculated using the specific gravity of the corresponding cream-base. A total of nine test units were prepared for each type of metered-dosing dispenser, three replicate test units for each of the 3 different cream-bases: thin, medium, and thick (Table 3).

DOSE MEASUREMENT

Dose measurements were conducted by weighing each prepared metered-dosing dispenser (without the protective cap) before actuation and then weighing again after dispensing a dose and wiping the dispensing port clean with a lint-free wipe. The test units were allowed to rest for a minimum of 2 hours between doses. This same procedure was repeated to measure 4 doses per day for a total of 60 doses or until no further cream-base could be dispensed with actuation. The final weights of the metered-dosing dispensers were then obtained to determine the amount of residual cream that was unable to be dispensed (Table 7). Dose measurements were converted to the volume amounts based on the specific gravity of each cream-base and were expressed in percentage of the target volume 0.5 mL/dose, as shown in the graphs of Figure 1.

RESULTS AND DISCUSSIONS

The net weight of each metered-dosing dispenser cream-base amount was converted to the volume amount (mL) for each group of metered-dosing dispensers (Table 4). This data represents the amount of cream-base in the metered-dosing dispensers after priming to approximately 30 mL filled amount for all test units with no overfill volume. It should be noted that each of the dispens-

TABLE 3. Experimental Parameters for Pump Dispenser Evaluation.

DISPENSER	ACTUATIONS PER 0.5-ML DOSE	NUMBER OF DOSES/ DAY	MINIMUM RESTING TIME (HRS.)	TOTAL NUMBER OF 0.5-ML DOSES PER DISPENSER	NUMBER OF UNITS TESTED (N/CREAM-BASE)	TOTAL UNITS TESTED (N/ DISPENSER)
Dispenser A (0.25)	2	4	2	60	3	9
Dispenser B (0.25)	2	4	2	60	3	9
Dispenser C (0.5)	1	4	2	60	3	9
Dispenser D (0.5)	1	4	2	60	3	9
Dispenser E (0.5)	1	4	2	60	3	9

ers can be filled beyond the 30-mL level but, to compare each of the dispensers equally, all were "primed" until approximately 30 mL were remaining in each dispenser. Dose uniformity (as specified below) was assessed based on the dispensed amount for the total 60 doses indicated in Table 3.

The metered-dosing dispensers' performances with each cream-base are profiled in the graphs shown in Figure 1.

Again, in order to compare each dispenser equally, there was no overfilling to compensate for the residual amounts of cream that could not be dispensed when near empty. Therefore, no metered-dosing dispenser completed a full 60 doses during the experiment. Normally, the metered-dosing dispensers would be overfilled to accommodate for the residual amounts (Table 7).

Actual and average volumes for the dispensed amounts at actuations "1 of 60," "30 of 60," and "50 of 60" are shown in Table 5. The number of doses found within specified limits for uniformity are presented in Table 6 for each test group, and calculated as percentage of the total 60 doses.

Individual dose uniformity is defined as an amount equivalent to 75% to 125% of the target dose, and the average amount for three replicate test units is within 85% to 115% of the target dose (as defined by the U.S. Food and Drug Administration's "FDA Draft Guidance for Industry").[9] Included in Table 7 is the amount of residual cream in the metered-dosing dispensers after no amount of cream-base could be further dispensed with actuation.

The performance of the different types of metered-dosing dispensers indicates the design differences may be significant. The properties of the cream-bases significantly impacted the amount dispensed for some of the airless-pump metered-dosing dispensers.

METERED-DOSING DISPENSER A (0.25-ML TOPI-CLICK)

The data shows that all Topi-CLICK test units accurately and precisely dispensed the cream-base within 75% to 125% of the target dose volume until 88.3% to 98.3% of the total 30 mL had been dispensed (Table 6; Figure 1). The performance of Topi-CLICK was not affected by the different types of cream-base. The entire range of the 88.3% to 98.3% of doses dispensed by Topi-CLICK units met the acceptance criteria for uniformity of doses (Tables 5-6).

After the Topi-CLICK's completed dispensing, the average amounts of residual cream were 2.3 mL to 2.5 mL (Table 7).

METERED-DOSING DISPENSER B (0.25-ML AIRLESS PUMP WITH COLLAPSIBLE POUCH)

The data shows that overdosing initially occurred with metered-dosing dispenser B when the packaged product was the "thin" cream-base. Multiple doses exceeded the upper limit of 115% of the target dose volume (Figure 1). The average volume for the dispensed amounts at actuation "1 of 60" was 118.1% of the target (Table 5). Additionally, underdosing developed after approximately 44 doses. The average volume for the dispensed amounts at actuation "50 of 60" was 53.5% of the target (Table 5). Due to the initial overdosing the airless-pump B prematurely dispensed below the lower limit of 85% (Figure 1). On average, only 45% of the total doses dispensed by pump B were within range for dose uniformity when using the "thin" cream (Table 6).

The "thick" cream-base had a similar effect on the performance of metered-dosing dispenser B, albeit to a lesser degree. Underdosing developed after approximately 47 doses (Figure 1). The range for average dispensing was 14.6% to 116.4% of the target 0.5-mL dose (Figure 1), and 76.7% of the total 60 doses were within range for dose uniformity (Table 6). Metered-dosing dispenser B improved with the "medium" cream-base where at least 80.0% of doses delivered were

TABLE 4. Beginning Volume (mL) of Cream-base After Priming in Dispenser.

DISPENSER A	FILLED DISPENSER WEIGHT (G)			DISPENSER WEIGHT AFTER PRIMING (G)			BEGINNING CREAM-BASE WEIGHT (G)			BEGINNING CREAM-BASE VOLUME (ML)		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	72.59	71.22	70.79	67.22	65.85	63.67	30.82	29.48	27.47	30.82	30.71	30.52
2	71.94	71.12	70.34	66.7	66.12	63.52	30.32	29.76	26.99	30.32	31	29.98
3	71.95	71.2	69.75	66.39	66.09	63.36	29.98	29.7	27.11	29.98	30.94	30.13
DISPENSER B	**FILLED DISPENSER WEIGHT (G)**			**DISPENSER WEIGHT AFTER PRIMING (G)**			**BEGINNING CREAM-BASE WEIGHT (G)**			**BEGINNING CREAM-BASE VOLUME (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	58.11	53.66	52.17	53.45	51.83	50.12	30.97	29.34	27.96	30.97	30.56	31.07
2	57.94	54.35	52.99	53.08	52.1	50.12	30.47	29.85	27.62	30.47	31.09	30.69
3	57.79	54.08	53.18	53.31	52.28	50.14	30.81	29.72	27.65	30.81	30.95	30.72
DISPENSER C	**FILLED DISPENSER WEIGHT (G)**			**DISPENSER WEIGHT AFTER PRIMING (G)**			**BEGINNING CREAM-BASE WEIGHT (G)**			**BEGINNING CREAM-BASE VOLUME (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	65.8	64.94	64.52	62.72	62.08	60.01	30.13	29.46	27.59	30.13	30.69	30.65
2	66.48	65.98	64.47	62.89	62.09	60.01	30.34	29.4	27.47	30.34	30.62	30.52
3	66.26	65.29	64.78	63.99	62.07	60.01	31.35	29.49	27.5	31.35	30.72	30.56
DISPENSER D	**FILLED DISPENSER WEIGHT (G)**			**DISPENSER WEIGHT AFTER PRIMING (G)**			**BEGINNING CREAM-BASE WEIGHT (G)**			**BEGINNING CREAM-BASE VOLUME (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	61.62	55.21	53.27	53.57	53.29	50.67	30.23	29.96	27.43	30.23	31.21	30.48
2	54.88	55.32	53.27	53.77	53.11	50.41	30.47	29.69	27.13	30.47	30.92	30.15
3	58.11	56.04	52.91	53.73	53.05	50.59	30.46	29.74	27.16	30.46	30.98	30.18
DISPENSER E	**FILLED DISPENSER WEIGHT (G)**			**DISPENSER WEIGHT AFTER PRIMING (G)**			**BEGINNING CREAM-BASE WEIGHT (G)**			**BEGINNING CREAM-BASE VOLUME (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	84.36	81.38	79.54	77.53	76.96	74.6	30.19	29.5	27.1	30.19	30.73	30.11
2	82.77	78.84	79.66	77.87	76.97	74.56	30.49	29.49	27.18	30.49	30.72	30.2
3	81.97	79.82	78.98	77.63	76.08	74.55	30.14	28.72	27.08	30.14	29.91	30.09

Note: Volume (mL) calculated based on cream-base specific gravity (see Table 2).

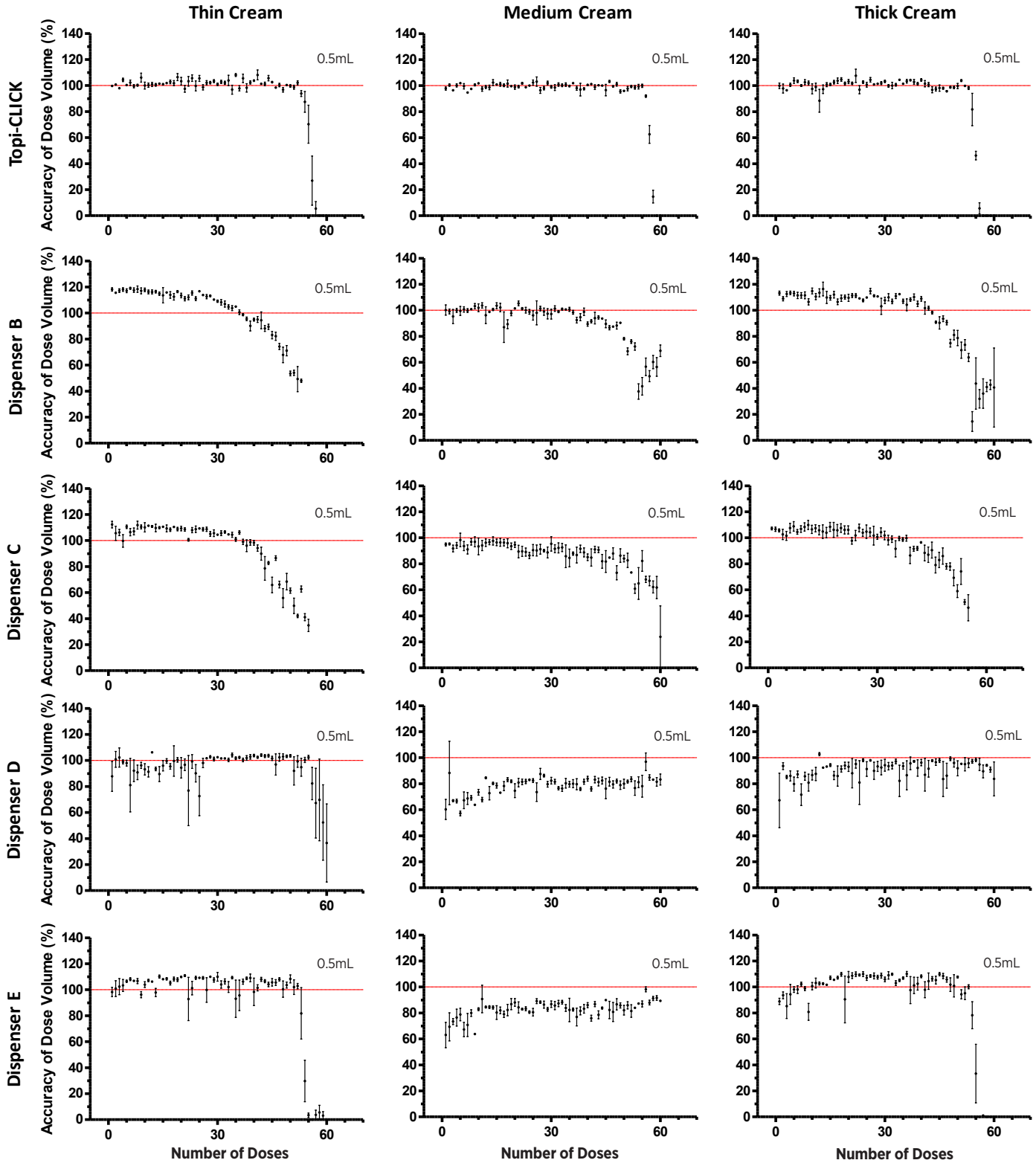
within the limits of 85% to 115%, and underdosing occurred after 50 doses or after approximately 81.7% of total doses had been dispensed (Table 6; Figure 1).

After the airless-pump B completed dispensing, the average amounts of residual cream were 2.0 mL to 3.6 mL (Table 7).

METERED-DOSING DISPENSER C (0.5-ML AIRLESS PUMP WITH COLLAPSIBLE POUCH)

Metered-dosing dispenser C operates the same as the airless-pump B with the exception that the target dose volume of 0.5 mL was dispensed with each actuation of the pump. Therefore, it was not unexpected to observe a similar performance profile between the two pumps. Although doses larger than 115% of target did not occur with metered-dosing dispenser C, the data shows that the patterns of dispenses were high for the first 30 doses with the "thin" cream-base (Figure 1). The average initial dose was 112.3% of target, and more than 100% of target for most of the first 30 doses (Table 5). Under-dosing developed after 42 doses or after approximately 70% of total doses had been dispensed (Figure 1). Similarly, the range of average dose was 97.7% to 109.9% of target in the first 50% of doses with the "thick" cream-base, and under-dosing occurred after approximately 75% of the total doses had been dispensed (Figure 1). The percentages of doses within range for dose uniformity were 71.7% and 75.0% for the "thin" and "thick" cream-base, respectively (Table 6). In contrast, the "medium" cream was dispensed at lower doses with higher

FIGURE 1. **Performance profiles of metered–dosing dispensers.**



Notes: Average dispensed amount in % relative to the target 0.5-mL dose volume for the total label number of doses. Error bars are standard deviations (n=3); horizontal line indicates 0.5 mL or 100% of target dose.

variability (dose range 23.8% to 98.3% of target), and 68.3% of doses were deemed within limits for dose uniformity (Figure 1; Table 6).

After the airless-pump C completed dispensing, the average amounts of residual cream were 3.8 mL to 4.5 mL (Table 7).

METERED-DOSING DISPENSER D (0.5-ML AIRLESS PUMP WITH PISTON)

The test results show that metered-dosing dispenser D was unsuitable for use with the "medium" cream-base, as a majority of doses were low and highly variable (Figure 1). Table 6 shows only 5.0% of total doses were within range for dose uniformity. Figure 1 shows average dispenses varied from 57.2% to 96.9% of the target dose. Metered-dosing dispenser D delivered a lower dose volume initially (Figure 1; Table 5), and the amounts of base dispensed were not consistent after approximately 78.3% to 83.3% of the total doses (Table 6). The range of average dispensed amounts were 36.6% to 104.3% and 67.2% to 102.7% of target dose volume for "thin" and "thick" cream-bases, respectively (Figure 1). However, more instances of underdosing were experienced using the "thick" than "thin" cream-base.

After the airless-pump D completed dispensing,

TABLE 5. Actual and average volumes for the dispensed amounts at actuations "1 of 60", "30 of 60" and "50 of 60".

DISPENSER A	VOLUME OF ACTUATION "1 OF 60" (ML)			VOLUME OF ACTUATION "30 OF 60" (ML)			VOLUME OF ACTUATION "50 OF 60" (ML)		
REPLICATES	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**
1	0.497	0.481	0.496	0.498	0.485	0.517	0.495	0.483	0.506
2	0.502	0.501	0.52	0.513	0.5	0.523	0.508	0.48	0.511
3	0.496	0.484	0.483	0.503	0.5	0.509	0.493	0.476	0.479
Average	0.498	0.489	0.5	0.505	0.495	0.516	0.499	0.48	0.499
% of Target	**99.70%**	**97.80%**	**99.90%**	**100.90%**	**99.00%**	**103.30%**	**99.70%**	**96.00%**	**99.70%**
DISPENSER B	**VOLUME OF ACTUATION "1 OF 60" (ML)**			**VOLUME OF ACTUATION "30 OF 60" (ML)**			**VOLUME OF ACTUATION "50 OF 60" (ML)**		
REPLICATES	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**
1	0.579	0.525	0.58	0.538	0.501	0.562	0.286	0.389	0.429
2	0.601	0.516	0.563	0.553	0.507	0.522	0.257	0.4	0.416
3	0.592	0.463	0.554	0.546	0.448	0.53	0.26	0.383	0.336
Average	0.591	0.501	0.566	0.546	0.485	0.538	0.268	0.391	0.393
% of Target	**118.10%**	**100.20%**	**113.20%**	**109.10%**	**97.10%**	**107.60%**	**53.50%**	**78.10%**	**78.70%**
DISPENSER C	**VOLUME OF ACTUATION "1 OF 60" (ML)**			**VOLUME OF ACTUATION "30 OF 60" (ML)**			**VOLUME OF ACTUATION "50 OF 60" (ML)**		
REPLICATES	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**
1	0.581	0.464	0.528	0.523	0.529	0.5	0.316	0.425	0.413
2	0.565	0.482	0.546	0.526	0.467	0.522	0.288	0.396	0.366
3	0.538	0.477	0.533	0.519	0.434	0.49	0.319	0.44	0.389
Average	0.561	0.474	0.536	0.523	0.477	0.504	0.308	0.42	0.389
% of Target	**112.30%**	**94.90%**	**107.10%**	**104.50%**	**95.30%**	**100.80%**	**61.50%**	**84.00%**	**77.90%**
DISPENSER D	**VOLUME OF ACTUATION "1 OF 60" (ML)**			**VOLUME OF ACTUATION "30 OF 60" (ML)**			**VOLUME OF ACTUATION "50 OF 60" (ML)**		
REPLICATES	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**
1	0.503	0.316	0.42	0.509	0.411	0.496	0.512	0.366	0.497
2	0.489	0.229	0.128	0.517	0.433	0.426	0.528	0.415	0.402
3	0.324	0.359	0.46	0.511	0.39	0.492	0.514	0.42	0.479
Average	0.439	0.301	0.336	0.512	0.411	0.471	0.518	0.4	0.459
% of Target	**87.70%**	**60.30%**	**67.20%**	**102.50%**	**82.30%**	**94.20%**	**103.60%**	**80.00%**	**91.90%**
DISPENSER E	**VOLUME OF ACTUATION "1 OF 60" (ML)**			**VOLUME OF ACTUATION "30 OF 60" (ML)**			**VOLUME OF ACTUATION "50 OF 60" (ML)**		
REPLICATES	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**	**THIN**	**MEDIUM**	**THICK**
1	0.504	0.37	0.423	0.516	0.433	0.542	0.516	0.389	0.546
2	0.513	0.357	0.446	0.563	0.455	0.512	0.569	0.396	0.537
3	0.456	0.218	0.464	0.57	0.413	0.533	0.54	0.447	0.533
Average	0.491	0.315	0.444	0.55	0.434	0.529	0.542	0.41	0.539
% of Target	**98.20%**	**63.00%**	**88.90%**	**109.90%**	**86.70%**	**105.90%**	**108.30%**	**82.10%**	**107.70%**

Notes: Average results are average of n=3 metered-dosing dispensers. Dispensed amounts determined as percentage of the target dose volume of 0.5 mL.

TABLE 6. Percentage of 60 Dispenses within Limits for Dose Uniformity after Primed to Approximately 30 mL.

DISPENSER	DOSES WITHIN UNIFORMITY LIMITS*		
	THIN	MEDIUM	THICK
Dispenser A (Topi-CLICK)	88.30%	96.70%	98.30%
Dispenser B	45.00%	80.00%	76.70%
Dispenser C	71.70%	68.30%	75.00%
Dispenser D	83.30%	5.00%	78.30%
Dispenser E	81.70%	38.30%	83.3.0%

*Table values are based on average of n=3 test units.

the average amounts of residual cream were 1.4 mL to 1.6 mL (Table 7).

METERED-DOSING DISPENSER E (0.5 ML AIRLESS-PUMP WITH PISTON)

The data show that metered-dosing dispenser E also was unfavorable for dispensing the "medium" cream-base, as only 38.3% of the total doses were within range for dose uniformity (Table 6). The average amounts varied between 63.0% to 90.8% of the target dose, and many dispenses failed the specified criteria for dose uniformity (Figure 1). There was minimal difference in metered-dosing dispenser E's performance with the "thin" and "thick" cream-bases, respectively, 81.7% and 83.3% of the total doses dispensed within range for dose uniformity (Table 6). An overdosing trend was observed with the "thin" and "thick" cream-bases (Figure 1).

After the airless-pump E completed dispensing, the average amounts of residual cream were 1.9 mL to 2.1 mL (Table 7).

CONCLUSION

Overall, the study shows Topi-CLICK performed with the best precision and accuracy compared to the four airless-pump metered-dosing dispensers. Most importantly, Topi-CLICK performance did not vary from one type of cream-base to the next. Therefore, Topi-CLICK was not affected by the variations in the cream-bases, and does not require further calibration prior to dispensing.

Most notable was that all four of the airless-pump metered-dosing dispensers exhibited greater dosage variation and sensitivity to the different properties in the three cream-bases than the Topi-CLICK. Therefore, airless-pump metered-dosing dispensers must be calibrated for each intended base or formula.[10]

Additionally noted, the two airless-pumps with collapsible pouch (metered-dosing dispensers B and C) demonstrated the most premature decline in overall dispensing. Both metered-dosing dispensers B and C had a characteristic of initial overdosing followed by underdosing with "thin" and "thick" cream-bases, but not with the "medium" cream-base.

Both airless-pumps with pistons (metered-dosing dispensers D and E) exhibited underdosing tendency with the "medium" cream-base, failing to dispense the label target volume within acceptable range. Even though the performance of airless-pump metered-dosing dispensers D and E was improved when dispensing the "thin" and "thick" cream-bases, the pump-to-pump variation may require each pump to be calibrated before dispensing, a time-consuming task in a busy pharmacy.

Regarding the residual cream-base amounts of all metered-dosing dispensers, the two airless pumps with piston (metered-dosing dispensers D and E) had the least amount of residual cream, followed by the Topi-CLICK and then the airless pumps with collapsible pouch, which had the most residual cream after completion. The residual cream that could not be dispensed is wasted product and represents added cost to manufacturing and to end users of the products.

REFERENCES

1. Kalorama Information Press Release (September 17, 2015). *Prescription Dermatological Drug Market Exceeds 21 Billion Dollars.* [Kalorama Information Website.] Available at: www.kaloramainformation.com/about/release.asp/id=3816. Accessed December 18, 2015.
2. Hellbardt S, Marx D. *Topical Trends–Trends in Skin Medication Dispensing.* Posted date September 5, 2013. [Drug Development & Delivery Website.] Available at: http://drug-dev.com/Main/Back-Issues/TOPICAL-Trends-in-Skin-Medication-Dispensin-620.aspx. Accessed November 30, 2015.
3. Meyer I. *Precise, Safe, and Convenient Airless Delivery of Dermal and Transdermal Formulations.* [Nemera Website.] June 2015. Available at www.nemera.net. Accessed December 17, 2015.
4. Del Rosso JQ. Evaluating topical drug delivery systems: The tube vs. the pump. 2007; 15(6). *The Dermatologist* 2007; 15(6). [The Dermatologist Website.] Available at: www.the-dermatologist.com/article/7333. Accessed November 30, 2015.
5. Topi-CLICK by DoseLogix. *Topical Metered-dosing Dispensers and Applicators.* [Topi-CLICK Website.] Available at: http://doselogix.com. Accessed November 30, 2015.
6. HUMCO Compounding. *SaltStable LO. Topical Compounding Bases.* [HUMCO Compounding Website.] Available at: http://humcocompounding.com/index.php/products/topical-bases/salt-stable-lo.html. Accessed October 7, 2015.
7. HUMCO Compounding. *PENCream. Topical Compounding Bases.* [HUMCO Compounding Website.] Available at: http://humcocompounding.com/index.php/products/topical-bases/pencreamtm.html. Accessed October 7, 2015.
8. HUMCO Compounding. *MultiBase. Topical Compounding Bases.* [HUMCO Compounding Website.] Available at: http://humcocompounding.com/index.php/products/topical-bases/multibasetm.html. Accessed October 7, 2015.
9. *Guidance for Industry—Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry, Manufacturing, and Controls Documentation. Draft guidance.* [FDA Website.] Available at: www.fda.gov/downloads/Drugs/.../Guidances/ucm070573.pdf. Note: Since no direct guidance could be found for metered-dose topical dispensers, these draft guidelines have been applied for analytical purposes for this study.
10. *Instructions for Airless-metered Dispensing Pumps* (#10393-5). Health Care Logistics, Inc. 2012. [Health Care Logistics Website.] Available at: www.GoHCL.com. Accessed December 18, 2015.

TABLE 7. Data of Remaining Residual Cream in Dispensers.

DISPENSER A	WEIGHT OF EMPTY DISPENSER (G)			FINAL WEIGHT OF DISPENSER AT COMPLETION (G)			REMAINING CREAM-BASE (G)			REMAINING CREAM-BASE (ML)		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	36.39	36.38	36.52	38.73	38.75	38.82	2.34	2.38	2.3	2.34	2.48	2.55
2	36.38	36.37	36.49	38.63	38.72	38.68	2.24	2.35	2.18	2.24	2.45	2.42
3	36.41	36.39	36.41	38.75	38.78	38.65	2.34	2.39	2.24	2.34	2.49	2.49
Average	36.39	36.38	36.47	38.7	38.75	38.72	2.31	2.37	2.24	2.31	2.47	2.49
DISPENSER B	**WEIGHT OF EMPTY DISPENSER (G)**			**FINAL WEIGHT OF DISPENSER AT COMPLETION (G)**			**REMAINING CREAM-BASE (G)**			**REMAINING CREAM-BASE (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	22.48	22.49	22.16	26.29	25.18	23.99	3.81	2.69	1.83	3.81	2.81	2.03
2	22.61	22.26	22.5	26.14	25.01	24.32	3.53	2.75	1.82	3.53	2.86	2.02
3	22.5	22.56	22.49	25.88	25.47	24.17	3.39	2.9	1.68	3.39	3.02	1.87
Average	22.53	22.44	22.38	26.1	25.22	24.16	3.58	2.78	1.78	3.57	2.9	1.97
DISPENSER C	**WEIGHT OF EMPTY DISPENSER (G)**			**FINAL WEIGHT OF DISPENSER AT COMPLETION (G)**			**REMAINING CREAM-BASE (G)**			**REMAINING CREAM-BASE (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	32.59	32.62	32.43	36.52	36.67	36.13	3.94	4.05	3.7	3.94	4.22	4.12
2	32.55	32.69	32.54	36.23	37.45	35.51	3.68	4.76	2.97	3.68	4.96	3.3
3	32.65	32.58	32.51	36.48	36.64	36.53	3.83	4.06	4.02	3.83	4.23	4.47
Average	32.6	32.63	32.49	36.41	36.92	36.06	3.82	4.29	3.56	3.82	4.47	3.96
DISPENSER D	**WEIGHT OF EMPTY DISPENSER (G)**			**FINAL WEIGHT OF DISPENSER AT COMPLETION (G)**			**REMAINING CREAM-BASE (G)**			**REMAINING CREAM-BASE (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	23.34	23.33	23.24	24.85	24.78	24.59	1.51	1.46	1.36	1.51	1.52	1.51
2	23.3	23.43	23.28	24.86	25.02	24.49	1.56	1.59	1.2	1.56	1.66	1.34
3	23.27	23.3	23.43	24.87	24.9	24.75	1.61	1.6	1.33	1.61	1.66	1.47
Average	23.3	23.35	23.32	24.86	24.9	24.61	1.56	1.55	1.3	1.56	1.61	1.44
DISPENSER E	**WEIGHT OF EMPTY DISPENSER (G)**			**FINAL WEIGHT OF DISPENSER AT COMPLETION (G)**			**REMAINING CREAM-BASE (G)**			**REMAINING CREAM-BASE (ML)**		
REPLICATES	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK	THIN	MEDIUM	THICK
1	47.34	47.46	47.49	49.08	49.41	49.27	1.74	1.94	1.78	1.74	2.02	1.97
2	47.38	47.48	47.37	49.4	49.51	48.99	2.02	2.03	1.61	2.02	2.12	1.79
3	47.49	47.37	47.47	49.31	49.39	49.15	1.82	2.02	1.68	1.82	2.1	1.87
Average	47.4	47.44	47.44	49.26	49.44	49.14	1.86	2	1.69	1.86	2.08	1.88

Note: Data represents amount of cream-base left in dispenser when no amount of cream-base can be further dispensed with actuation. Volume (mL) calculated based on cream-base specific gravity (see Table 2).

Address correspondence to Nicole Vu, PhD, Analytical Research Laboratories, Inc., 840 Research Parkway, Suite 546, Oklahoma City, OK 73104. E-mail: nvu@arlok.com