GlobePharma

Innovating the Industry Standard.

DYNASEG™

(Patent Pending)

Segregation Testing Under Dynamic & Stressed Conditions

Content Uniformity Issues?

Optimizes Blend Formulation & Process

Avoiding **Segregation** Problems in Production

ProQbD™

Quality by Design

EXECUTIVE SUMMARY

An innovative apparatus, "**DYNASEG**™ (Patent Pending), and method for segregation testing of powder blends is presented, enabling determination of segregation potential under dynamic stressed conditions. **DYNASEG**™ empowers pharmaceutical formulation scientists to evaluate, during the formulation development stage, which powder blend formulations are most resistant to segregation during large-scale manufacturing. By identifying robust formulations at the formulation development stage, manufacturers can mitigate content uniformity failures and align with the "Quality by Design" (QbD) principles for consistent, cGMP compliant production. This apparatus would be especially needed in the development of robust solid formulations of low dose drug products.

Dynamic testing of several powder blends, using low dose acetaminophen as a model drug for low dose directly compressible formulations, revealed that the formulation variables such as particle size, excipient bulk density and drug loading, as well as process parameters such as intensifier type, intensifier speed and blending method strongly influence segregation potential. For instance, micronized acetaminophen consistently produced more robust blends compared to non-micronized powder, while microcrystalline cellulose-rich formulations resisted segregation better than those containing mixtures of microcrystalline cellulose and dicalcium phosphate dihydrate. Similarly, the choice of blending intensifier was critical—SIFT-N-BLEND® technology consistently outperformed high-speed and pin intensifiers, particularly at low drug loading or reduced intensifier speeds.

The results obtained using the **DYNASEG**™ apparatus highlight the limitations of conventional content uniformity testing of samples taken from a static powder bed. Although several formulations passed content uniformity specification using samples from a static powder bed, many of them failed the content uniformity specification when samples are taken from a dynamic powder bed using the **DYNASEG**™ apparatus. The **DYNASEG**™apparatus is unique, compared to other devices available in the market for segregation testing, in that it subjects the powder sample to a combination of four

mechanisms for segregation – gravity flow (flow through a tube), obstruction to flow (baffles), fluidization of the powder (when powder falls from one baffle on to the next one) and vibration (the tube is attached to a vibration device), which are characteristic of large-scale manufacturing. This emphasizes the importance of dynamic segregation testing for predicting real-world performance of powder blends.

This apparatus is portable, requires only a small sample size (about 30cc), takes less than 10 minutes to run a test, and can be used in a fume hood or a glove box for testing blends of highly potent APIs, which require containment, for protection of the operators. In addition, cleaning between tests is simple as it is easy to disassemble the parts.

It is recommended that the solid dosage formulations and the processing parameters be optimized at the formulation development stage itself using the **DYNASEG**™apparatus to avoid costly content uniformity problems in manufacturing.

BACKGROUND

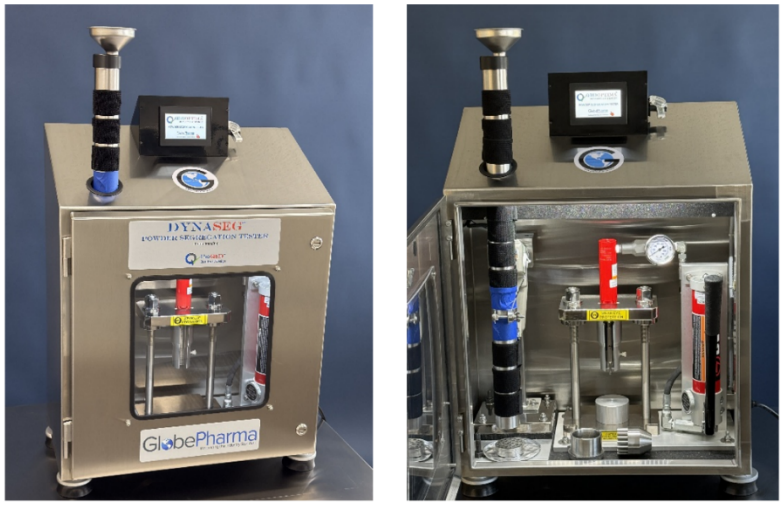
A powder blend is a heterogeneous product and tends to segregate, especially when it is flowing while discharging from a blender, from a hopper to a machine such as a tableting machine or a capsule filling machine, a powder-filling machine, mechanical or pneumatic conveying, etc. A blend which does not segregate even under such stressed dynamic conditions is dynamically stable. In other words, such a blend is stable under conditions characteristic of production-scale processes.

When a static powder blend is tested for content uniformity, it may pass the content uniformity specifications, but it may fail if tested under stressed dynamic conditions. When only static powder bed content uniformity testing is done, it is often experienced in the industry that such products stand a chance of failing content uniformity specifications under stressed dynamic conditions characteristic of the manufacturing operations. Several pharmaceutical manufacturers have been cited by FDA for blend and dosage form content uniformity non-compliance.

DESCRIPTION

DYNASEG™ dynamic powder segregation tester (Patent Pending) from GlobePharma is a result of 32 years of research and five prototypes.

This apparatus has a stainless tube with multiple baffles mounted inside at an angle to allow the powder to flow by gravity over one baffle on to the next one and so forth and collect onto a split sample die with 30 unit-dose cavities. The powder thus collected on the die is scraped evenly with a spatula, and the unit-dose powder samples in the die cavities are compacted into tablets using a manual tablet compaction machine, which is a part of the apparatus. The test parameters can be set using the HMI (human-machine interface).



DYNASEG™
Dynamic Powder Segregation Tester

Powder samples in the die cavities may be compacted individually using a standard tablet punch or all the samples at once using a custom-made multiple-tip punch. The compressed tablets are ejected from the top segment of the split die either individually with the standard punch or all the tablets at once by using the custom-made multiple-tip punch. These tablets are now analyzed separately for content uniformity of the active ingredient by UV spectrophotometry, HPLC, UPLC or process analytical technology (PAT) as appropriate for the given drug candidate.

The technique of having unit-dose samples in the form of compacts is critical to minimize any error caused by the powder sampling technique and handling of the loose powder samples in the analytical laboratory, especially with low dose directly compressible formulations.

Additional stress may be added to the gravity flow of the powder sample over baffles to further challenge the powder blend's resistance to segregation under stressed conditions. In this apparatus, a vibration device is provided to subject the stainless-steel tube with baffles to different levels of controlled vibration while the powder sample flows through the tube over the baffles. Different formulations and blending process variables may be tested with this apparatus for segregation potential of powder blends, and the one which resists segregation the most under stressed conditions will most likely not cause any segregation problems on production scale machines. This is the whole concept of this apparatus, which is the result of 32 years of research and 5 prototypes!

FORMULATIONS TESTED ON DYNASEG™

Several formulations of acetaminophen were made to mimic low dose formulations, covering the effect of the following experimental variables, and tested for segregation behavior:

1. *Type of blending intensifier attachment used* – SIFT-N-BLEND® (SNB), high-speed intensifier bar (HSI), and pin intensifier bar (PIN)
2. *Speed of the intensifier attachment* – 1500, 1000, and 500 rpm
3. *Type of blending technique* – dry blending and wet blending
4. *Dose of micronized acetaminophen per tablet* – 0.5 mg and 0.1 mg per 125 mg tablet
5. *Particle sizes of acetaminophen powder* – micronized with mean particle size of 7 µm (Mallinckrodt Pharmaceuticals, New Jersey, USA) and non-micronized with particle sizes of <63 µm (71.2%), 63-250 µm (26.6%), and >250 µm (2.2%) (Granules India Limited, Telangana, India), and
6. *Types of filler binder used with very different bulk densities* – Microcrystalline cellulose and dicalcium phosphate dihydrate (unmilled), individually and in combinations of different proportions.

BLENDING PROCESS

GlobePharma's MaxiBlend® lab blender (**Fig.1**) with a 4-quart stainless steel V-shell (shown below is the blender with a 16-quart acrylic shell for

transparency), equipped with one of the three intensifier attachments – SIFT-N-BLEND® (**Fig.2A**), high-speed intensifier bar (**Fig.2B**) or pin intensifier bar (**Fig.2C**) was used. The blender shell speed was fixed at 25 rpm and the intensifier was run at the speed specified in the title of the respective graphs. Total dry blending time was 20 minutes – 5 minutes pre-blending without using the intensifier, 10 minutes using the intensifier and 5 minutes with the lubricant without using the intensifier. For wet blending, the excipients, except the lubricant, were pre-blended for 5 minutes, acetaminophen was added in the form of an alcoholic solution while blending (wet blending), the wet blend was dried in an oven at 60°C, re-loaded into the blender and blended for 10 minutes using the intensifier at the specified speed and 5 minutes with the lubricant without using the intensifier.

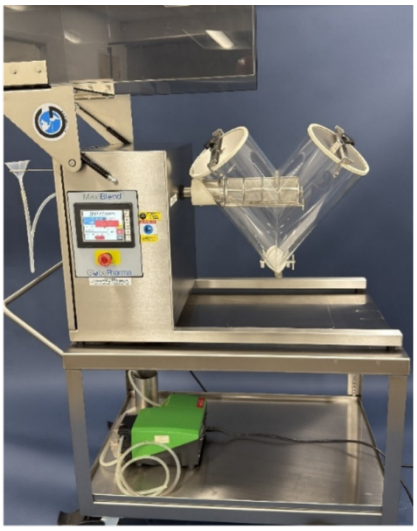


Fig. 1: MaxiBlend® Lab Blender
(shown with an acrylic shell fitted with SIFT-N-BLEND® intensifier)

GlobePharma's Patented (US 8,235,582; US 8,827,545; CA 2736942C; CA 2821188C & EP2703072B1) SIFT-N-BLEND® technology facilitates simultaneous sifting and blending in the blending vessel itself eliminating the need for separate sifting of ingredients, such as silicon dioxide, and provides excellent content uniformity of pharmaceuticals, especially low dose ones, as well as food and cosmetic ingredients such as colors, flavors, sweeteners, etc. because of multiple-time sifting of the powder blend while mixing. Small amount of liquids may also be added through the intensifier.

Fig. 2A: SIFT-N-BLEND®

Fig. 2B: High-speed I-Bar

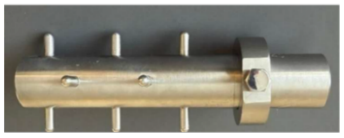


Fig.2C: Pin I-bar

DYNASEG™ DYNAMIC POWDER SEGREGATION TESTING PROCEDURE

This test method involves the following steps:

1. A split sample die with 30 unit-dose cavities is placed under the stainless tube of the apparatus.
2. The level of vibration to be used is selected (i.e., GFOB+V20 or GFOB+V30 or GFOB+V40) using the HMI on the apparatus, if vibration is to be applied to the tube, and vibrator is activated.
3. A 30cc sample of the powder blend is added to the funnel at the top of the tube; the powder sample passes over a series of baffles inside the tube and collects on to the split die at the bottom.
4. The excess powder on the split die is scraped with a spatula. The die is then placed on a compaction block under the punch holder of the manual tablet compaction machine (MTCM-II, Patent US 6,585,507).
5. Appropriate tablet punch is inserted into the punch holder and the powder samples in all the cavities on the die are compacted into tablets of required hardness either one by one using the standard tablet punch or all at once using a custom-made multiple-tip punch.
6. The top part of the split die is separated from its base, placed on an ejection cup and the tablets are ejected by using MTCM-II either one by one with the standard tablet punch or all at once by with the custom-made multiple-tip punch.
7. The tablets are then analyzed for content uniformity using a suitable analytical method, such as UV spectrophotometry, HPLC, UPLC, PAT, etc., as appropriate for the drug being evaluated.
8. Five replicate tests are done in each experiment, ANOVA statistical analysis was done, and the results are shown in Figures 3-10.
9. A tube cleaning procedure was adopted before each run by selecting the cleaning mode in the HMI. If thorough cleaning was required, it could be easily carried out, as the system allows for quick and simple disassembly of parts.

Key for the Graphs:

SNB-DRY: SIFT-N-BLEND® dry blend; HSI-DRY: high-speed intensifier bar, dry blend; PIN-DRY: pin intensifier bar, dry blend; SNB-LIQ: SIFT-N-BLEND®, wet blend; HSI-LIQ: high-speed intensifier bar, wet blend.
B: baseline; GFOB: gravity flow over baffles; GFOB+V20: gravity flow over baffles with added vibration at level 20; GFOB+V30: gravity flow over baffles with added vibration at level 30; GFOB+V40: gravity flow over baffles with added vibration at level 40.
Error bars in the graphs represent standard error. Different letters above data points indicate statistically significant differences at $p < 0.05$ (*), $p<0.01$ (**), and $p < 0.001$ (***) using ANOVA. The red horizontal dotted line in the graphs shows 6% CV cutoff mark for acceptable content uniformity (C.U).

RESULTS

Segregation behavior of micronized acetaminophen in powder blends with 0.5 mg acetaminophen per dose prepared by dry blending technique with different types of intensifier attachments

Fig. 3 shows the dry blends prepared by using SIFT-N-BLEND® and the high-speed intensifier bar at 1500 rpm are similar in their resistance to segregation.

The significantly higher segregation potential of powder blends prepared with a pin intensifier bar indicate that these powder blends may not hold up well during subsequent manufacturing operations, such as tableting, encapsulation or powder filling into pouches or jars.

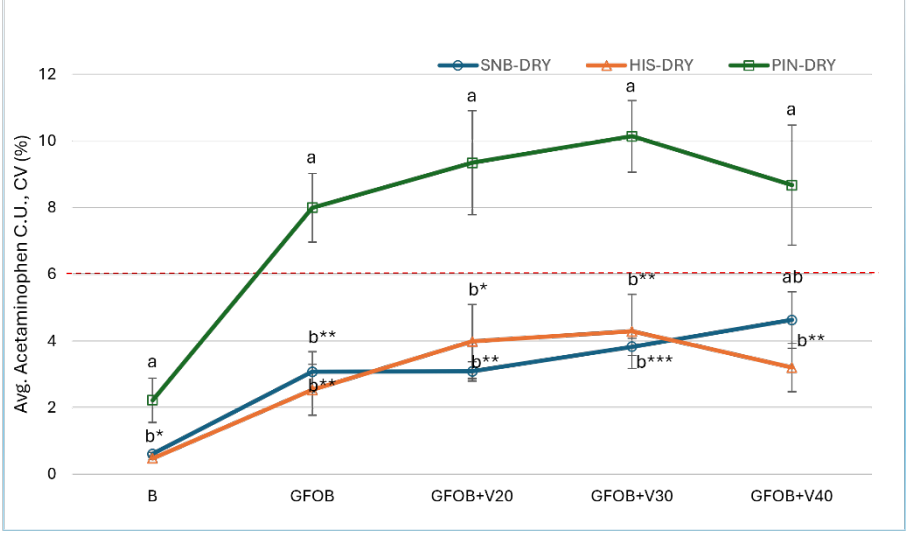


Fig. 1: Average content uniformity of acetaminophen in powder blends with 0.5 mg acetaminophen per dose, prepared at 1500 rpm and subjected to segregation potential testing using **DYNASEG™** powder segregation tester. Error bars represent standard error. Different letters above data points indicate statistically significant differences at $p < 0.05$ (*), $p<0.01$ (**), and $p < 0.001$ (***) using ANOVA with Tukey's HSD.

An important result to be noted is that the three formulations have acceptable baseline (static) acetaminophen content uniformity and, without dynamic segregation testing, may mislead the formulator to think that all the formulations meet USP specification of not more than 6% CV in content uniformity, while, in fact, the formulation made with pin intensifier bar may not retain its content uniformity under dynamic conditions encountered in manufacturing operations.

Segregation behavior of micronized acetaminophen in powder blends with 0.5 mg of acetaminophen per dose prepared by dry blending techniques at intensifier speed of 1000rpm and 500rpm

As seen from **Fig. 4,** both SIFT-N-BLEND® and the high-speed intensifier bar, at 1000 rpm speed, performed similarly with no statistically significant difference at any test condition. However, the coefficient of variation is higher at all test conditions compared to the coefficient of variation results at 1500 rpm (FIG.16), indicating that content uniformity of the blend is getting worse as the intensifier speed is reduced from 1500 rpm to 1000 rpm.

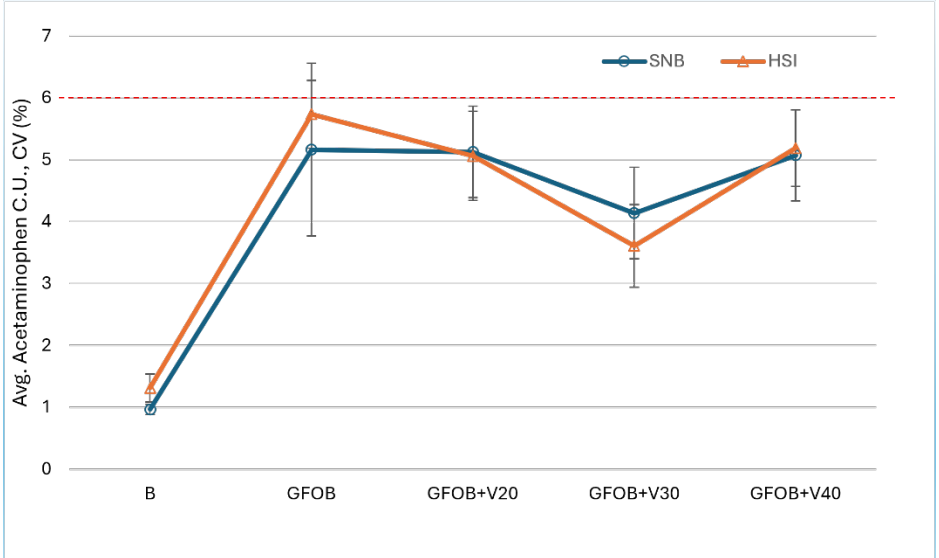


Fig. 4: Average content uniformity of acetaminophen in powder blends with 0.5 mg acetaminophen per dose, prepared at 1000 rpm and subjected to segregation potential testing using **DYNASEG**™ powder segregation tester. Error bars represent standard error.

Fig. 5 shows that both SIFT-N-BLEND® and the high-speed intensifier bar, at 500 rpm speed, performed poorly, with content uniformity getting further worse, compared to 1000 rpm speed. It should be noted that both the blends passed the content uniformity specification at baseline (static blend), misleading that that 500rpm speed is good enough, while both the blends failed upon dynamic testing, although SIFT-N-BLEND®

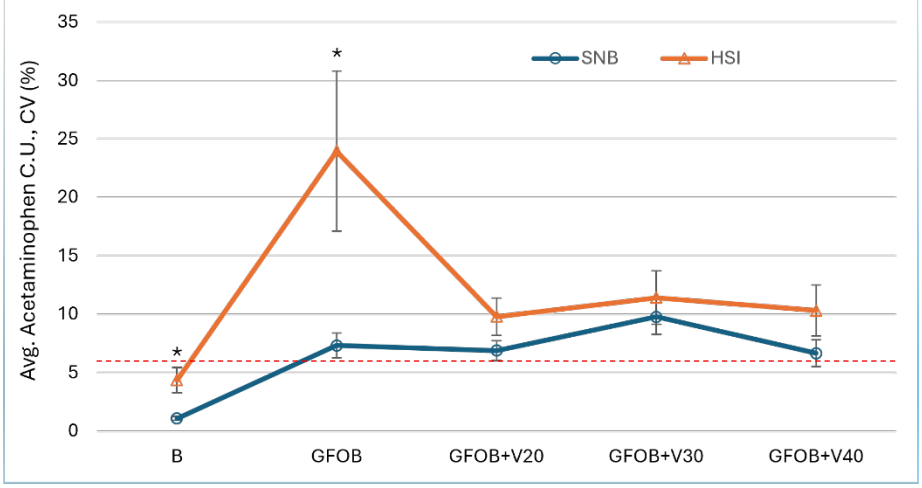


Fig. 5: Average content uniformity of acetaminophen in powder blends with 0.5 mg acetaminophen per dose, prepared at 500 rpm and subjected to segregation potential testing using **DYNASEG**™ powder segregation tester. Error bars represent standard error, and statistically significant differences were represented at $p < 0.05$ using ANOVA.

performed significantly better ($p<0.05$) than the high-speed intensifier bar at the baseline as well as gravity flow over baffles. It can be concluded from these results that a minimum speed of 1000 rpm is needed to achieve acceptable content uniformity of acetaminophen.

Segregation Behavior of Micronized and Non-micronized Acetaminophen in Powder Blends with 0.5 mg of Acetaminophen per Dose and Prepared by Dry Blending using SIFT-N-BLEND® and high-speed intensifier bar

As can be seen from **Figs. 6 and 7**, blends prepared with micronized acetaminophen powder resisted segregation at all the levels of segregation testing conditions with both SIFT-N-BLEND® and the high-speed intensifier bar and maintained content uniformity within the USP specification of not more than 6% CV, whereas the blends prepared with non-micronized acetaminophen powder failed USP specification for blend content uniformity at all segregation testing conditions, except the baseline (static blend). It is important to note that at baseline, the content uniformity of the blend prepared with the non-micronized acetaminophen powder passed the USP specification, which may mislead a formulator to accept such a blend, unless dynamic segregation testing is done using the powder segregation tester of the present invention.

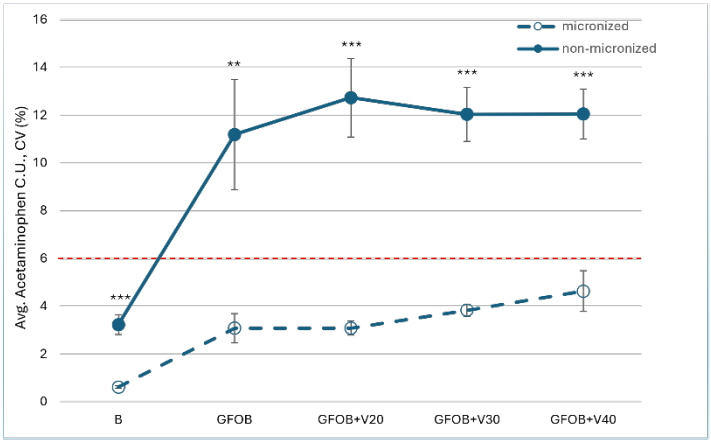


Fig. 6: Average content uniformity of acetaminophen in powder blends with 0.5 mg acetaminophen per dose prepared using **SIFT-N-BLEND®** by different particle size of API at 1500 rpm speed and subjected to segregation potential testing using **DYNASEG™** powder segregation tester. Error bars in the graphs represent standard error. Different letters above data points indicate statistically significant differences at $p < 0.05$ (*), $p<0.01$ (**), and $p < 0.001$ (***) using ANOVA.

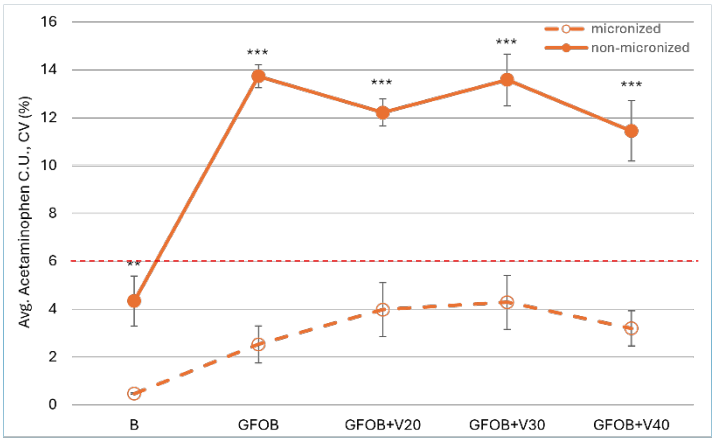


Fig. 7: Average content uniformity of acetaminophen in powder blends with 0.5 mg acetaminophen per dose prepared using high-speed intensifier bar by different particle size of API at 1500 rpm speed and subjected to segregation potential testing using **DYNASEG™** powder segregation tester. Error bars in the graphs represent standard error. Different letters above data points indicate statistically significant differences at $p < 0.05$ (*), $p<0.01$ (**), and $p < 0.001$ (***) using ANOVA.

Segregation behavior of micronized acetaminophen in powder blends with 0.5 mg of acetaminophen per dose prepared by dry blending technique using SIFT-N-BLEND® at intensifier speed of 1500rpm using a combination of two fillers of different bulk densities in different ratios

Fig. 8 shows how mixtures of MCC and DCP in different ratios affect the segregation behavior of acetaminophen in the resulting powder blends. The only blend which resisted segregation at all test conditions was the one with 100% MCC (A).

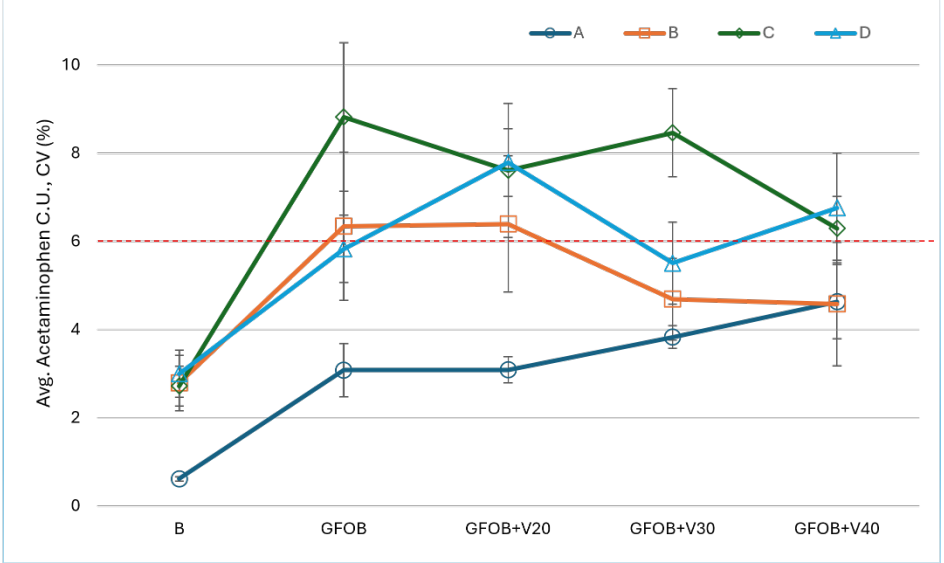


Fig. 8: Average content uniformity of acetaminophen in SNB blends with 0.5 mg acetaminophen per dose, prepared by different ratios of MCC and DCP at 1500 rpm intensifier speed and subjected to segregation potential testing using **DYNASEG™** powder segregation tester. Error bars represent standard error. A- MCC:DCP (100:00), B- MCC:DCP (60:40), C- MCC:DCP (40:60), D- MCC:DCP (00:100).

The other three blends failed the content uniformity specification at all the test conditions, except the baseline (static bed), misleading the formulator that the formulations are good if dynamic testing is not done. It should also be noted that these three blends also showed highly variable results at all the stressed test conditions, compared to the formulation with 100% MCC (A). It can be inferred from this experiment that it may not be a good idea to use combination of fillers with very different bulk densities, and DCP is not a choice filler.

Segregation Behavior of Micronized Acetaminophen in Powder Blends with a Very Low Dose (0.1mg) of Acetaminophen per Dose and Prepared by Dry Blending Techniques

As can be seen from **Fig. 9**, the blend prepared with the SIFT-N-BLEND® technique stayed dynamically very stable up to vibration level V30, while the blend prepared with the high-speed intensifier bar technique started to lose dynamic stability at all conditions of testing. Thus, SIFT-N-BLEND® technique provided a more dynamically stable blend than the high-speed intensifier bar, even with a very low dose formulation of acetaminophen.

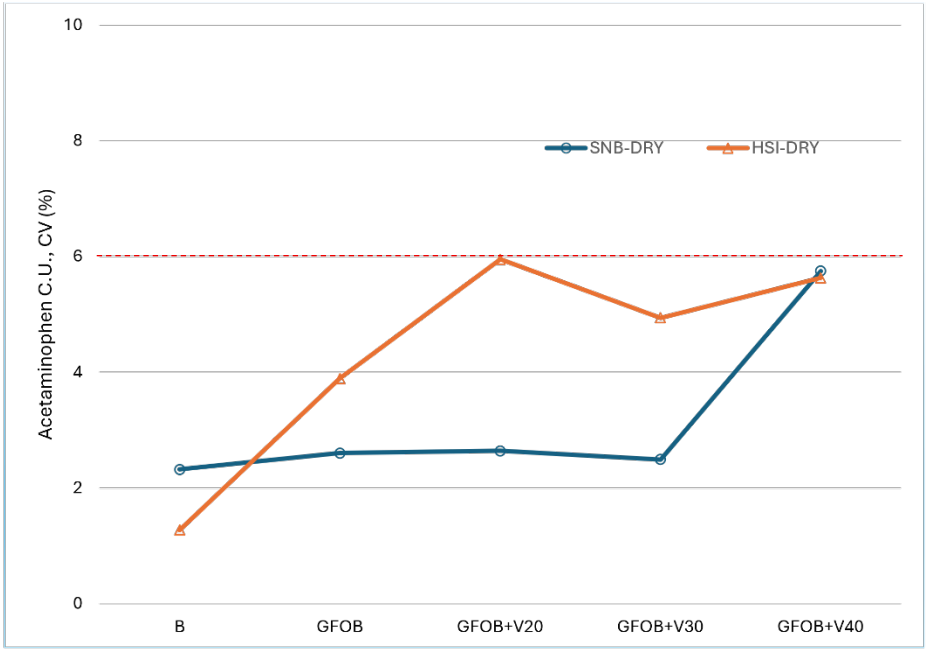


Fig. 9: Content uniformity of acetaminophen in powder blends with 0.1 mg of acetaminophen per dose, prepared by different dry blending techniques at 1500 rpm and subjected to segregation potential testing using **DYNASEG**™ powder segregation tester.

Segregation Behavior of Acetaminophen in Powder Blends with 0.5 mg of Micronized Acetaminophen per Dose and Prepared by Wet Blending Techniques Using SIFT-N-BLEND® and High-speed Intensifier Bar

As can be inferred from Fig. 10, both the wet blends, prepared by SIFT-N-BLEND® and the high-speed intensifier bar, remained dynamically stable after segregation testing at all the test conditions, with the CV remaining much below 6%, and there is no statistically significant difference between the CV values obtained in this experiment with SIFT-N-BLEND® and the high-speed intensifier bar. Thus, adding the drug in the form of a solution while blending may provide the most stable blend.

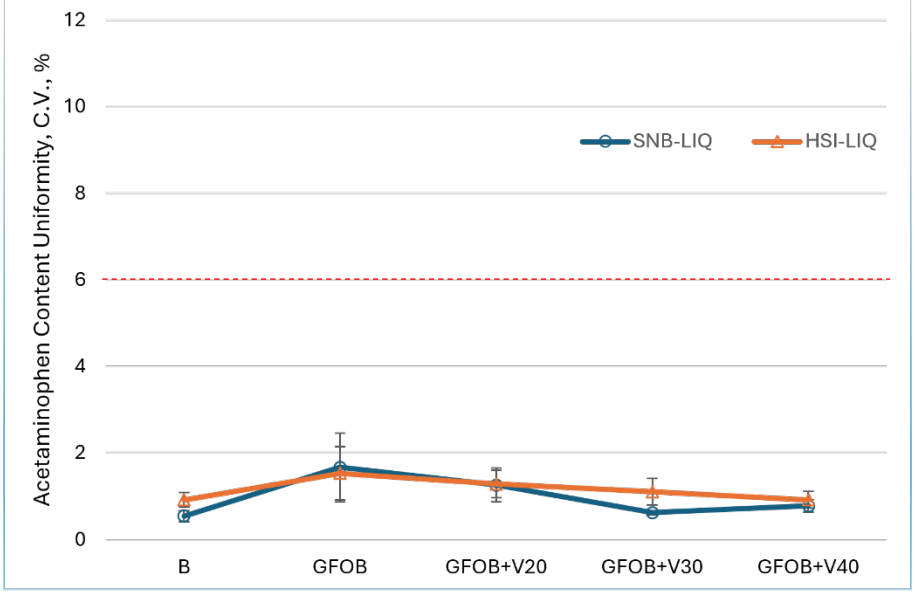


Fig. 10: Content uniformity of acetaminophen in powder blends, with 0.5 mg acetaminophen per dose, prepared by wet blending in a V-shell on a lab blender using SIFT-N-BLEND® and high speed intensifier bar at 1500 rpm, and subjected to segregation testing using **DYNASEG™** powder segregation tester.

DISCUSSION

The results obtained using the **DYNASEG™** apparatus clearly highlight the limitations of conventional content uniformity testing of a sample from a static powder bed. Although several formulations passed content uniformity specification under static conditions, they exhibited significant segregation under stressed dynamic conditions, which are characteristic of large-scale manufacturing. This emphasizes the importance of dynamic segregation testing for predicting real-world performance of powder blends.

Dynamic testing revealed that the formulation variables such as particle size, excipient bulk density and drug loading, as well as process parameters such as intensifier type, intensifier speed and blending method strongly influence segregation potential. For instance, micronized acetaminophen consistently produced more robust blends compared to non-micronized powder, while MCC-rich formulations resisted segregation better than those containing mixtures of MCC and DCP. Similarly, the choice of blending intensifier was critical—SIFT-N-BLEND® technology consistently outperformed high-speed and pin intensifiers, particularly at low drug loading or reduced intensifier speeds.

The introduction of controlled vibration during testing further challenges the blend robustness. This feature of **DYNASEG™** provides a realistic stress-testing framework that pharmaceutical manufacturers can use to identify critical failure points early in development.

CONCLUSION

DYNASEG™ Dynamic Powder Segregation Tester is an essential apparatus for identifying robust formulations at the formulation development stage so that manufacturers can mitigate blend/dosage form content uniformity failures and align with the "Quality by Design" (QbD) principles for consistent, cGMP compliant commercial product manufacturing, enabling the proactive selection of robust formulations and reducing the risk of FDA citations for blend uniformity failures.

The **DYNASEG™** equipment is a compact, benchtop, and portable model, making it suitable for placement inside an enclosed and properly ventilated hood or a glove box, for testing highly potent compounds, which require containment, to ensure adequate protection for the operator. In addition, it requires a small sample for testing, takes less than 10 minutes to run a sample, and is easy to clean between tests.

RECOMMENDATION

Optimize your solid dosage formulation and the processing parameters at the formulation development stage using **DYNASEG**™ Dynamic Powder Segregation Tester so that you can avoid costly content uniformity problems in manufacturing.

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