

Hashim Ahmed, Ph.D. and Navnit Shah, Ph.D.
Pharmaceutical and Analytical R&D, Hoffmann-La Roche Inc., Nutley NJ

Formulation of Low Dose Medicines - Theory and Practice

Progress in pharmaceutical research has produced very potent drugs, which require careful formulation and production in order to produce solid oral dosage forms with acceptable homogeneity and physical stability. Assuring the physical stability of a powder blend for production of tablets or capsules represents a major quality assurance consideration. The content uniformity quality control procedure for most tablets and capsules which are the subject of official monographs is by the analysis of mean drug content of 20 tablets which have been ground together (B.P., 1973). Train (1960) realizes that such an assay procedure could provide a satisfactory mean value, even though individual tablets showed large variations about the mean. The B.P. recognized the importance of the problem when in 1973 it introduced a requirement of individual tablet assay for "microdose" preparations (tablets containing less than 2 mg or 2% w/w of active drug). As well as specific problems associated with interpretation of the data, which such assays, provide (Orr and Sallam, 1978); there are also more general problems such as inability to detect batches where loss of homogeneity has occurred up until the testing of the finished product. Secondly, such late testing provides no information concerning the point of failure nor the mechanism by which content uniformity has been lost. In order to solve both specific and general problems associated with current pharmacopeial testing, a simple reproducible and informative test is required, by which tablet content uniformity under realistic processing conditions can be assessed. This test should have the following criteria (Staniforth et al, 1989):

1. Ability to be performed on powder mixes prior to processing
2. It should reflect actual homogeneity likely to be encountered in the ultimate dosage forms produced

3. Ability to be used as a pre-formulation/formulation problem solving tool, to screen potential formulations at an early stage or as in-process quality assurance test prior to compaction or encapsulation
4. Reproducibility and simplicity for use as a routine test during quality assurance procedures

It is clear from the above criteria that the test method of choice should subject powder mixes to conditions, which reflect the most rigorous process conditions, which the powder mix will encounter during production. Powder systems which pass a sufficiently validated test procedure would then be considered to be physically stable, non-segregating and capable of producing tablets and capsules of high uniformity.

The objective of the present study was to achieve optimum homogeneity and physical stability (resistance to segregation) for a low dose formulation (0.07% w/w) by comparing the use of 3 different tablet excipients: Lactose Anhydrous (LA), Starch 1500 (STA) or Microcrystalline Cellulose (MCC). A specially designed segregation cell was described and used in this study to assess powder mixes physical stability prior to production.

Materials

- Model Drug: the active bulk drug substance 50th percentile = 8.9 μm .
- Lactose Anhydrous: as a tablet filler.
- Starch, Direct Compression Grade (Starch 1500): as a disintegrant and a binder.

- Microcrystalline Cellulose (Avicel PH 102): Directly compressible excipient.
- Magnesium Stearate: as a lubricant.

Methods

Experimental batches were prepared by mixing the active drug substance with a portion of either Lactose Anhydrous (LA), Microcrystalline Cellulose (MCC) or Starch 1500 (STA) and milled using a FitzMill through # 000 plate, impact forward at medium speed, in order to achieve distribution of the drug in the premix. The resultant premix was further mixed with the remainder of the excipient used and the other formulation ingredients (except for the lubricant) for 15 minutes and passed through a # 0 plate, knives forward at medium speed. Magnesium stearate was added and mixed for 5 minutes. The final granulation was compressed on a high-speed tablet press (Manesty B3B) equipped with 3/16" standard concave punches. Content uniformity studies were carried out on the experimental batches produced.

CONTENT UNIFORMITY AND SEGREGATION STUDIES OF THE FINAL POWDER MIXTURES AND TABLETS

Content Uniformity of the Final Powder Mixture

Content uniformity testing was carried out by withdrawing at least 10 random samples using a sampling thief from different parts of the final powder mixture contained in the twin shell blender according to a validated sampling scheme. This scheme was adopted because it allows sample selection from: top, center, bottom and wall locations. In other words, it offers random representation of the entire powder blend. Samples selected were tested for their drug contents using an HPLC stability-indicating method.

Content Uniformity of the Tablets

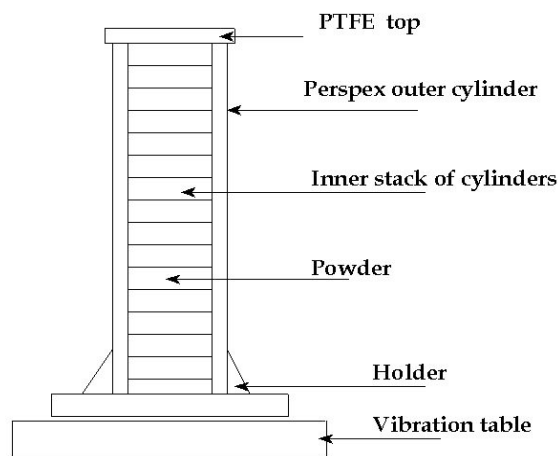
Tablets were randomly selected from the beginning, middle and end of each compression run. 30 tablets were tested for their content uniformity using the HPLC stability-indicating method mentioned above.

Segregation Studies

The segregation tendency was investigated using a special segregation cell (Figure 1).

This is represented by a special arrangement of stacking per-

Figure 1: A stack of Perspex Cylinders used a Part of the Segregation Cell



- Final powder blends were loaded (50 g) inside the cell
- Cell was clamped on a vibrating Tapping Density tester which vibrates at 4Hz
- Following vibration powder inside the cell was sampled consecutively
- Samples weighing 170 mg were selected and tested for drug content

spx (plastic) cylinders used to sample powder mixtures following stress under vibration. Powder mixture sampled randomly from the twin shell blender ((50 g) was loaded into the segregation cell. The loaded segregation cell was then clamped to a Tapping Density Tester (from Vanderkamp) capable of applying low frequency vibration of 4Hz which mimics the vibration expected during tableting. 100 cycles of tapping were applied during the test. Following tapping, powder inside the perspex stacks was sampled consecutively using a spatula. Samples weighing 170 (1 mg (this corresponds to the tablet weight i.e. the scale of scrutiny) were tested for their drug contents using an HPLC stability-indicating method similar to the one used for testing powder mixtures and tablets.

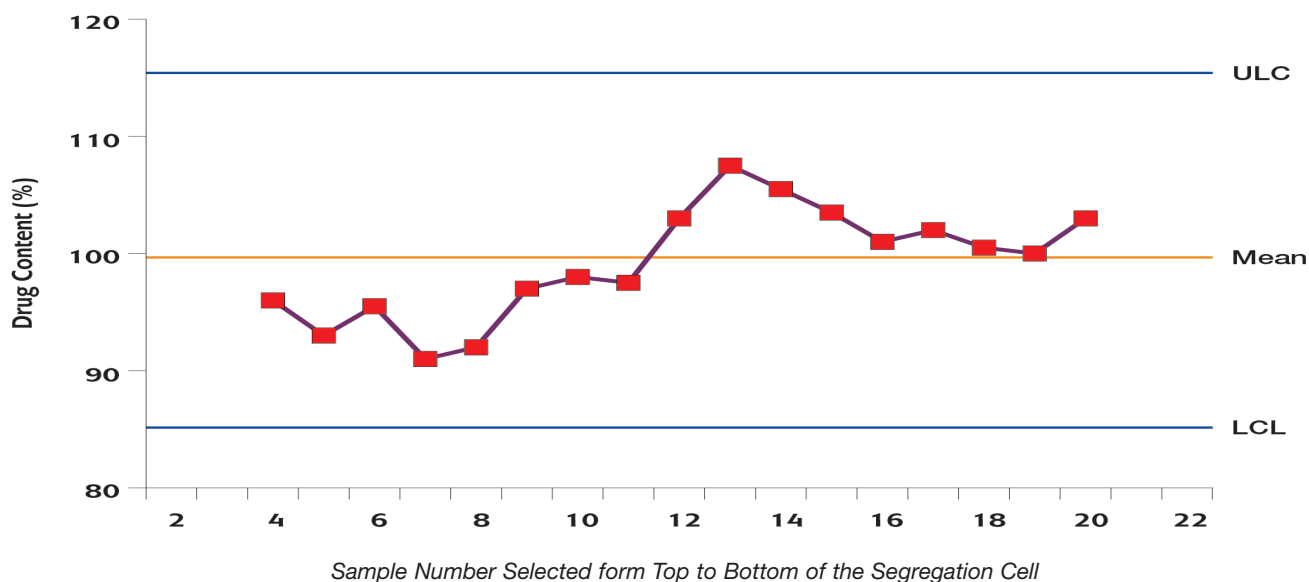
Results and Discussion

Content uniformity data for the 3 formulations prepared using LA, STA or MCC as carriers for preparing active-premix are shown in Table 1.

Table 1: Data for Initial Experimental Studies

Excipient used for Active-Premix Preparation	Batch Size (Number of Tablets)	Content Uniformity Mean Drug Content (%) ±RSD	
		Final Powder Blend	Tablets
Lactose Anhydrous	200,000	82.20 ± 4.61	92.43 ± 1.42
Starch 1500	200,000	90.65 ± 3.89	96.00 ± 1.25
Avicel PH 102	200,000	98.52 ± 3.98	99.59 ± 3.19

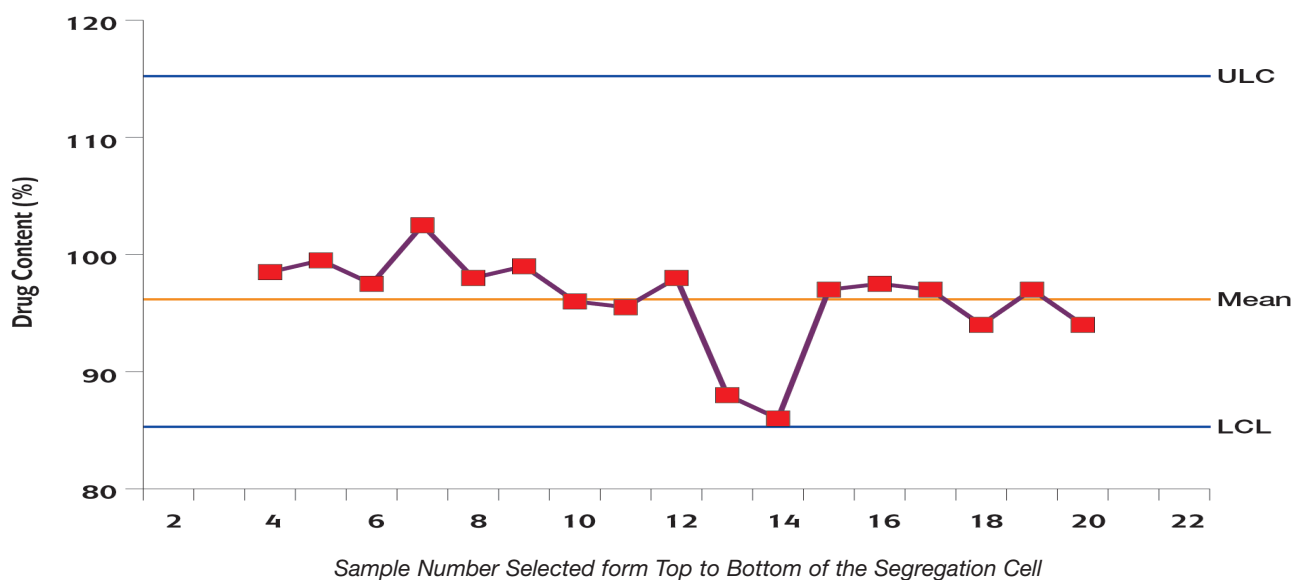
Figure 2: Segregation Profile for the Formulation Prepared with Lactose Anhydrous as a Carrier for the Active-Premix (RSD = 4.75%)



From the experimental data shown in Table 1, it is apparent that differences in RSD of the final powder were not significant when the active-premixes were prepared using either LA or STA; however, the difference in the mean drug content was significant. The batch produced using LA for its premix preparation had a lower mean drug con-

tent for both the final powder blend and the tablets than the one produced using STA for its premix preparation. The batch produced using MCC for its premix preparation had an RSD of 3.19% for the tablets while the batch produced using STA for its premix had an RSD of 1.25%. The lower the RSD the better is the content uniformity of the

Figure 3: Segregation Profile for the Formulation Prepared with Microcrystalline Cellulose (Avicel PH 102) as a Carrier for the Active-Premix (RSD = 4.26%)



Reprinted from [American Pharmaceutical Review](#), Volume 3 Issue 3
 For further information please contact: Russell Publishing LLC
 Tel: 317-816-8787 Fax: 317-816-8788 Email: nm@russpub.com

powder mixture or tablets.

These findings were further supported by the segregation studies using the special segregation cell described above. Figures 2, 3 and 4 show the segregation profiles (after vibration) for the 3 powder mixtures prepared using LA, MCC and STA, respectively. In these segregation studies the drug concentration was determined at each level of the vibrated cylinder (Figure 1), and the difference from the overall sample mean was used to assess the drug distribution throughout the vibrated cylinder. The relationship between the drug content and specific parts of the powder bed was shown by plotting deviations from the sample mean at different levels of the cylinder where samples were selected. The segregation profile for the formulation prepared using LA as carrier for active-premix (Figure 2) showed a tendency for the upper parts of the powder bed to become depleted in drug content.

The drug depletion at the top of the powder bed was probably caused by the increased percolation of particles due to vibration. This has resulted in an RSD of 4.75%. The segregation profile for the formulation prepared using MCC (Figure 3) shows an accumulation of the drug at the upper parts of the powder inside the vibrated cylinder. This may have been caused by movement of coarser carrier particles (rich in adherent drug particles) to the upper parts of the powder bed. This has resulted in an RSD of 4.26%.

Figure 4 shows the segregation profile for the formulation prepared using STA for the active-premix. In this case no drug depletion or drug migration to the upper parts of the powder bed was observed. The RSD was equal to 3% following vibration.

These quantitative data were also supported qualitatively by scanning electron micrographs (SEMs) which confirmed the formation of an ordered (adhesive) mix when Starch 1500 was used as the excipient for the premix preparation. The fact that Starch 1500 produces homogeneous mixes may be related to its superior adhesive characteristics resulting from its pregelatinized nature and inherent high moisture (about 10%). The effect of moisture on forming stable and homogeneous adhesive powder mixes can be attributed to hydrogen bond formation due to the highly polar water molecules, where water may undergo chemisorption as well as physisorption (Gregg and Sing, 1982). The apparent role of moisture in the formation of strong adhesive units suggested that, in some respects, the phenomenon of ordered mixing could be considered to be a form of spontaneous granulation driven by free energy changes (Staniforth, 1985).

Production-size batches (4,000,000 tablets) of this product were manufactured using Starch 1500 as the carrier for preparing the active-premix. Tablets produced indicated superior content uniformity (Mean drug content = 99%, RSD = 2%; Figure 5).

Conclusions

1. Formulation of low dose medicines can be very challenging and problems related to content uniformity and physical stability may arise and need to be controlled.
2. Rationale selection of excipients for the specific steps during formulation/process development is a critical factor to be considered to develop a homogeneous and segregation-free low dose formulation.

References

1. Gregg S.J. and Sing. K.S. W. (1982). Adsorption, Surface Area and Porosity. 2nd Edition London: Academic Press.
2. Orr, N.A. and Sallam, E.A. (1978). Content uniformity of potent drugs in tablet. *J. Pharm. Pharmacol.* 30, 741-747.
3. Staniforth J.N, Ahmed, H.A. and Lockwood, P.J. (1989) Quality assurance in pharmaceutical powder processing: Current developments. *Drug. Dev. & Ind. Pharm.* 15 (6&7), 909-926.
4. Staniforth J.N., (1985). "Ordered Mixing or Spontaneous Granulation", *Powder Technol.* 40, 73-77
5. Train, D. (1960). Pharmaceutical aspects of mixing solids. *Pharm. J.* 185, 129-134

Figure 4: Segregation Profile for the Formulation Prepared with Starch 1500 as a Carrier for the Active-Premix (RSD = 3%)

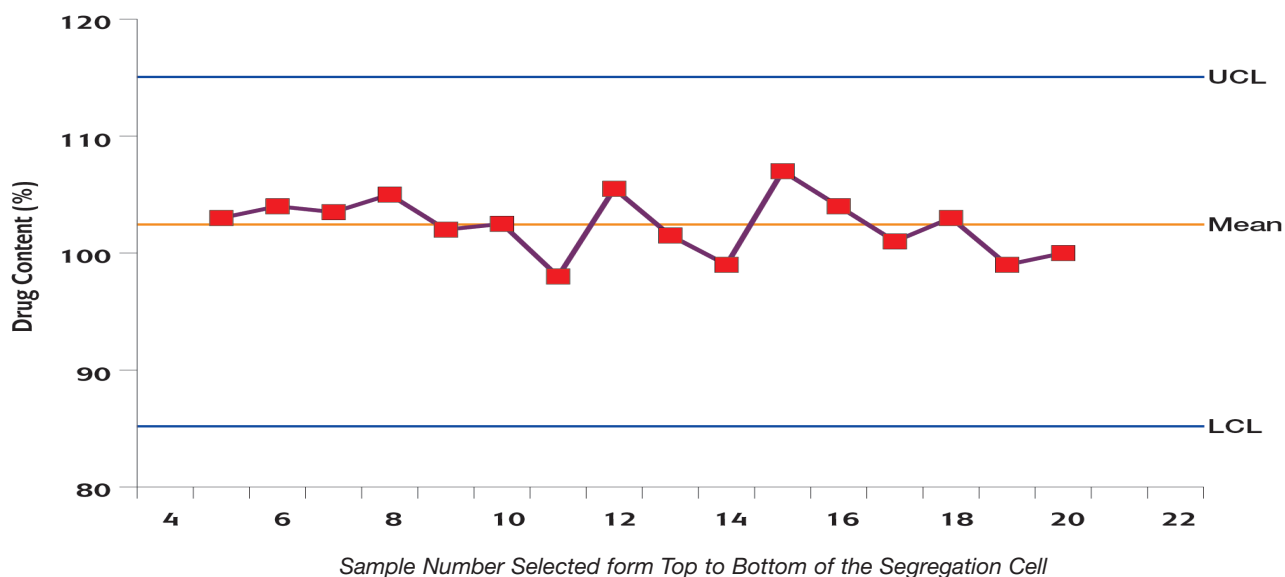


Figure 5: Drug Content vs. Sample Number for the Production Batch Manufactured (RSD = 2%).

