Asian Journal of Chemistry Vol. 20, No. 3 (2008), 1741-1749

Regulatory Requirements of In Process Content Uniformity - A Practical Approach

K. KATHIRESAN*, R. SRINIVASAN, K. KANNAN, P. PANDIAN,
S. SELVAMUTHUKUMAR and R. MANAVALAN
Department of Pharmacy, Annamalai University
Annamalai Nagar-608 002, India
Tel: (91)9443402296; E-mail: kathiresan123@rediffmail.com

Blending is one of the most important unit operations in preparation of tablets and the end point of this process to be evaluated by sampling the blend and performing the offline analysis. These schedules are made in order to establish the uniformity and homogeneity of the blend and provide a platform for the validity. It gives a degree of confidence that the blend when compressed into tablet will give an output of uniform dosage units. These schedules were used only to provide confidence in the processing. However, today with the advent of theories such as process capabilities and the lesser importance to retrospective validation and more learning towards continual validated state, the need to shift strategies are prevalent. The FDA guidance on content uniformity 2003 provides such a platform. The guidance is being widely used in the assessment during the processing of exhibit/submission batches since 2004. This is the first time that the guidance has been employed for commercial product also. The primary objective of this project work is to asses the blend uniformity with three validation batches and establishing the adequacy of mixing for the product. To prove that the data of blending and compression is uniform and the process of blending and compression is within the control from the batches manufactured commercially.

Key Words: Regulatory, Process, Uniformity.

INTRODUCTION

One of the most common unit operations in preparation of tablets is the physical blending of the active drug substance with one or more excipents. The end point of this process is the material homogeneity as measured by sampling and offline analysis of the powder. Removal of samples is covertly done with a sampling probe called a 'thief 'to withdraw a sample[1]. 'Thief' is a probe designed to extract and collect small volumes of powder from a chosen representative cross section of blender. The resulting samples are then assayed using the same method used to analyze the finished product. 'Content Uniformity' is established if the drug content of the samples conforms to predetermined criteria[2,3]. This method is influenced by the skill of the operator and often provides false representation of sample due to desegregation and disruption of the powder bed

during sampling and transport. Thus, both sampling and analytical error are likely to incur in these sampling procedure. So validation is mandatory, FDA's 2003 guidance to industry to amend the good manufacturing practice regulation, commercial batch final blend need to be tested routinely for blend homogeneity. Three factors can directly contribute to content uniformity problems *i.e.*, (i) non-uniform distribution of drug substance through out the powder mixture or granulations, (ii) segregation of the powder mixture or granulation during various manufacturing process and (iii) tablet weight variation. A solid dosage form less than 50 % active or 50 mg active that the USP would require the content uniformity testing on the drug product.

Objective of this work is to asses the blend uniformity with three validation batches and establishing the adequacy of mixing for the product. To prove that the data of blending and compression is uniform and the process of blending and compression is within the control from the batches manufactured commercially.

Challenges of blend uniformity testing for tablet formulation

The first step in evaluating the blend uniformity is to obtain the representative sample using good sampling device. A statistically representative sample is random sample, which has the same composition of each component as it is in the blend or any other samples[4,5]. Unfortunately, it is not technically feasible at this time to consistently obtain the representative blend samples of 1-3 times the unit dosage weight primarily due to blend sampling errors. Blend sampling errors could come from the design of the sampling thief, the sampling technique, physical/chemical properties of the formulation, material transfer and analytical procedures. A sample removed from the blend may not have exactly the same composition as all other samples taken from the blend because powders usually segregate to some degree due to differences in the flow properties of the individual components in the blend. The design of the sampling thief (shape, length, number of sampling chambers) may affect how the individual components flow into the cavities and the amount of overall blend flow into cavities.

The sampling technique is crucial in determining if the samples adequately represent the blend. The insertion orientation, insertion angle, insertion depth and the operator differences, such as force and smoothness of motion, may significantly impact the consistency of sampling. The formulation factors that may contribute to the blend sampling errors include the compressibility, compatibility, flow ability, surface area, inter particle force, lubricity, particle size distribution, density and the drug load in the formulation[6,7]. Furthermore, the post blending transfer and storage process could have impact on the blends, such as potential segregation. Although blend uniformity may be evaluated by extensive sampling throughout the blender, further sampling from intermediate bulk containers may also be important.

Simple conversion between lot *vs.* sample statistics in pharmaceutical dosage uniformity

This article describes the estimation of population mean from sample data. Population mean may be estimated as upper and lower limits[8,9]. For example, on 95 % confidence interval[10,11] using MS Excel, the upper and lower limits for a sample (n = 10) with mean, say 98 % LC and SD, say 3.5 % LC:

Upper limit = 98+ TINV(0.025×10^{-1}) × $3.5/10^{0.5}$ = 100.97 % LC

Lower limit = 98- TINV(0.025×10^{-1}) × $3.5/10^{0.5}$ = 95.03 % LC

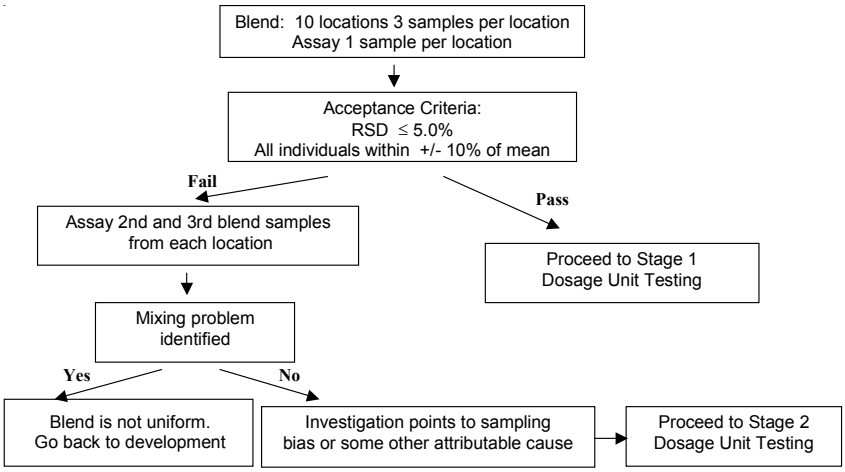
where, TINV(0.025×10^{-1}) = t score at 95 % confidence, two ailed, with 10^{-1} or 9 degree of freedom.

$10^{0.5}$ = square root of 10 (sample size n = 10)

Product taken for this study: Product taken for this study is citalopram HBr tablets 10/20/40 mg. This citalopram HBr tablet is for oral administration contains 10, 20 and 40 mg of citalopram and other inactive ingredients like lactose mono hydrate (diluent), MCC (diluent), corn starch (diluent), crosscarmellose sodium, copolyvidone (binder), glycerin, magnesium stearate (lubricant) and colloidal silicon dioxide (glidant)[12-15].

Statistical review and process capability measurements of commercial batches

The commercial batches above all strength, citalopram HBr 40 mg is the highest strength and it was taken for the process capability studies (Fig. 1, Tables 1 and 2). In order to study the process capability the mean values should be normally distributed and within control. Hence the normal probability graph and X bar (mean)/range chart was prepared for blend stage (Figs. 2-4) and finished stage (Figs. 5-7) then the process capability study was carried out on the commercial batches.



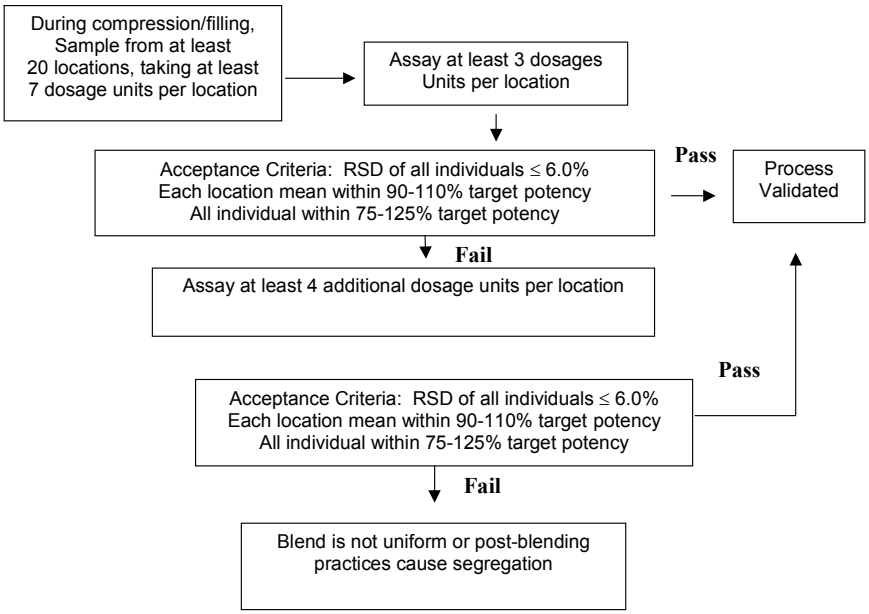


Fig. 1. Schematic representation of validation approach

TABLE-1
CONTENT UNIFORMITY RESULTS OF THREE VALIDATION
BATCHES FOR CITLOPRAM HBr tablet 40 mg

Location / St ages	Batch I			Batch II			Batch III		
	Dry mixing	Blending	From SS Bins	Dry mixing	Blending	From SS Bins	Dry mixing	Blending	From SS Bins
1	98.7	102.5	100.7	10.1.9	99.2	99.6	101.0	100.8	100.5
2	99.2	97.5	101.4	101.5	99.0	99.8	99.4	100.2	99.8
3	100.1	97.4	102.0	103.4	99.7	99.3	97.8	98.4	101.9
4	98.8	100.7	100.3	102.1	99.0	101.4	99.0	98.9	98.4
5	99.0	100.1	96.5	102.8	101.0	100.5	97.5	99.5	99.5
6	103.1	98.0	102.5	101.7	101.3	101.6	98.4	100.6	98.8
7	98.9	100.3	102.5	102.6	98.8	101.9	98.5	100.3	99.5
8	99.8	100.5	98.3	101.8	100.3	100.2	99.0	103.3	101.0
9	99.7	101.5	100.8	102.6	104.0	99.9	98.2	98.8	100.1
10	99.6	101.0	104.1	99.6	101.8	101.3	99.1	97.8	100.2
Mean	99.7	100.0	100.9	102.0	100.4	100.6	98.8	99.9	100.0
RSD	1.3	1.7	2.2	1.0	1.7	0.9	1.0	1.0	1.0

TABLE-2
STRATIFIED SAMPLING RESULTS OF CITALOPRAM HBr 40 mg

Batch I				Batch II				Batch III			
Sample no.	Results	Wt. Corrected	Mean	Sample no.	Results	Wt. Corrected	Mean	Sample no.	Results	Wt. Corrected	Mean
1	97.9	96.8	95.6	1	95.6	100.2	99.5	1	97.0	97.6	97.8
	96.2	95.3			98.9	99.4			96.8	98.6	
	94.8	94.8			97.1	98.9			96.7	97.1	
2	96.1	94.9	96.4	2	99.4	100.9	100.5	2	99.8	98.3	98.2
	97.9	96.8			99.6	100.7			97.5	99.3	
	97.6	97.5			98.5	99.8			98.1	97.1	
3	94.0	94.0	94.9	3	100.8	103.0	99.3	3	100.0	98.6	98.4
	96.0	94.9			98.0	99.3			99.6	98.5	
	96.6	95.7			100.1	95.7			99.3	98.1	
4	99.1	97.7	99.0	4	97.7	96.5	99.3	4	97.1	97.7	97.8
	99.5	99.3			99.7	101.8			98.7	98.0	
	100.2	100.0			98.4	99.7			97.3	97.6	
5	97.6	97.2	97.0	5	101.3	101.2	100.6	5	96.7	99.3	98.4
	97.0	96.7			97.7	98.8			98.7	97.3	
	97.4	97.2			98.6	101.7			98.3	98.4	
6	97.0	96.6	96.2	6	97.8	99.6	100.1	6	97.8	98.8	98.5
	97.2	96.0			98.7	95.3			97.7	98.6	
	95.9	95.9			101.2	105.5			98.8	98.2	
7	98.1	97.9	98.1	7	96.1	99.8	99.2	7	96.9	99.3	99.1
	97.9	97.8			97.3	99.5			97.8	98.7	
	98.6	98.7			97.7	98.3			99.6	99.4	
8	96.9	96.5	97.7	8	96.3	97.3	99.2	8	98.3	98.2	98.3
	99.5	98.1			98.2	100.3			99.7	97.5	
	98.8	98.4			99.2	99.8			98.8	99.1	
9	96.7	95.7	96.7	9	98.4	101.3	101.0	9	99.7	99.6	99.8
	98.8	97.9			98.7	100.1			98.6	100.0	
	98.6	96.4			100.1	101.5			99.5	99.7	
10	96.7	94.2	95.7	10	98.2	100.4	98.3	10	97.0	96.4	97.6
	96.1	96.8			98.3	98.5			97.2	97.8	
	97.2	96.1			96.3	96.1			98.2	98.5	
11	95.1	94.5	96.8	11	97.9	100.9	100.5	11	100.5	100.9	99.2
	97.5	97.8			98.6	97.9			97.6	99.0	
	97.4	98.2			101.4	102.7			97.9	97.8	
12 (S1)	97.4	98.4	97.3	12 (S1)	96.0	98.7	100.7	12 (S1)	98.7	99.8	99.9
	96.1	95.5			100.7	101.6			98.0	99.6	
	99.2	98.1			98.5	101.9			100.3	100.2	

Batch I				Batch II				Batch III			
Sample no.	Results	Wt. Corrected	Mean	Sample no.	Results	Wt. Corrected	Mean	Sample no.	Results	Wt. Corrected	Mean
13 (S2)	100.0	99.2	100.3	13 (S2)	98.4	100.4	99.1	13 (S2)	96.9	98.2	98.9
	104.0	104.2			98.3	100.4			97.6	98.9	
	96.6	97.4			95.8	96.5			98.0	99.6	
14 (S3)	96.8	98.2	98.0	14 (S3)	97.1	98.7	99.2	14 (S3)	98.2	98.0	99.2
	96.6	96.3			96.9	100.4			99.0	98.9	
	100.3	99.4			98.0	98.4			100.1	100.8	
15	97.1	96.1	96.5	15	98.9	100.5	100.2	15	98.1	97.5	97.9
	98.3	97.2			97.1	98.1			97.8	98.1	
	98.0	96.3			99.5	101.9			99.0	98.2	
16	95.3	94.9	96.3	16	98.1	101.3	98.6	16	99.0	99.9	99.9
	97.9	97.5			97.0	98.0			97.4	99.1	
	98.4	96.6			97.9	96.6			99.9	100.5	
17	98.9	97.2	95.3	17	99.5	100.8	100.1	17	99.6	100.3	98.5
	96.3	94.9			101.2	101.6			96.5	95.9	
	95.2	93.7			99.4	97.8			99.9	99.3	
18	97.0	97.2	97.4	18	98.0	100.6	101.3	18	100.5	101.7	100.6
	96.1	97.0			100.3	104.5			100.3	101.9	
	96.8	98.1			99.4	98.9			98.2	98.1	
19	97.7	96.1	96.5	19	97.6	100.2	98.9	19	98.4	99.0	97.5
	96.4	97.0			98.7	98.1			99.3	98.8	
	98.0	96.4			97.4	98.5			97.0	94.8	
20	94.5	94.8	96.7	20	96.5	98.2	98.3	20	99.6	101.5	98.2
	96.4	97.2			96.0	96.9			96.7	96.1	
	98.4	98.0			99.1	99.6			96.9	96.9	
RSD		1.8		RSD	2.0			RSD	1.4		

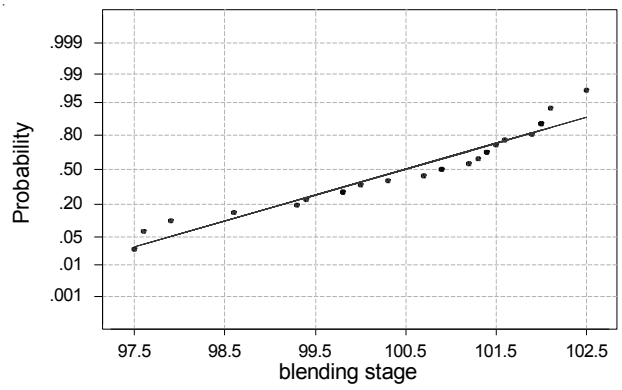


Fig. 2. Normal probability plot at blending stage for citalopram HBr 400 mg

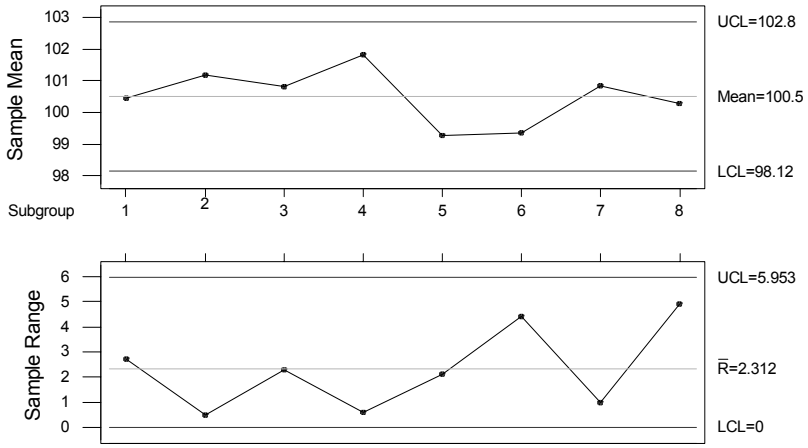


Fig. 3. Xbar/R Chart at blending stage for citalopram HBr 40 mg

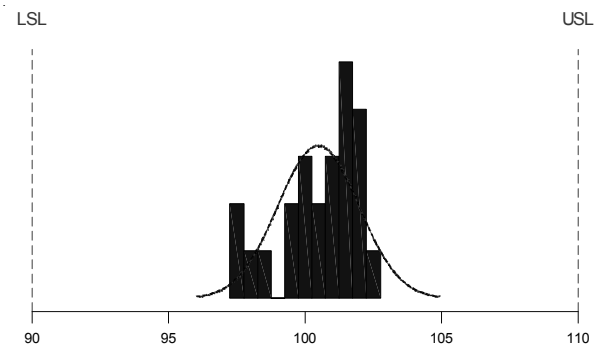


Fig. 4. Process capability analysis at blending stage for citalopram HBr 40 mg

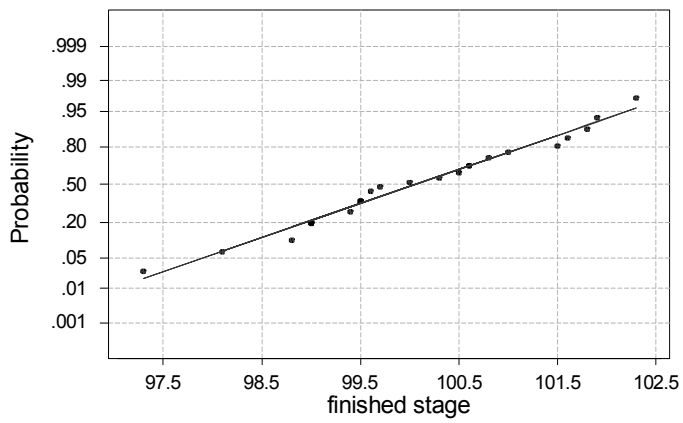


Fig. 5. Normal probability plot at finished stage for citalopram HBr 40 mg

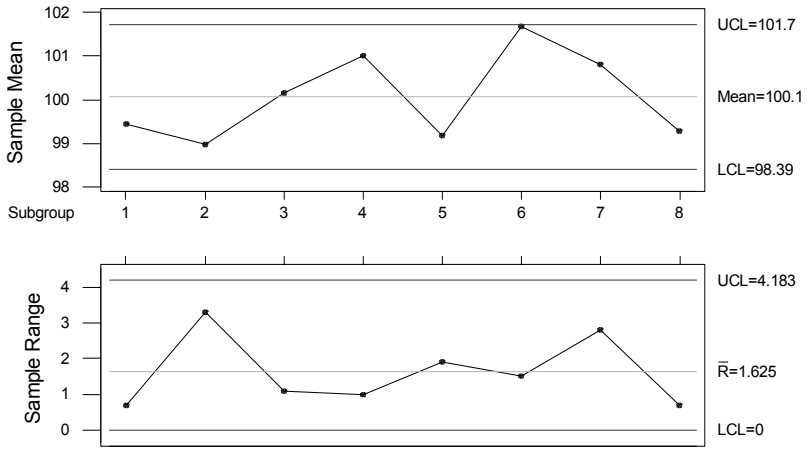


Fig. 6. Xbar/R chart at finished stage for citalopram HBr 40 mg

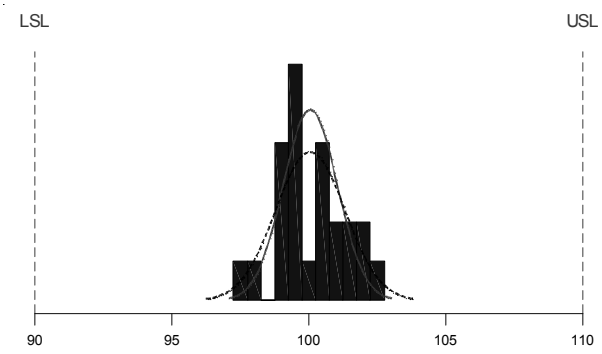


Fig. 7. Process capability analysis at finished stage for citalopram HBr 40 mg

Conclusion

This work is based on the FDA's draft guidance to assess the adequacy of mixing to meet the blend uniformity criteria. The sampling method was planned and performed to meet the requirements for assessment of adequacy of mixing. The commercial batches of blend data and finished data of citalopram HBr 40 mg were taken for process capability studies at both blend and finished stage. Hence this data ensures that adequacy of uniform mixing at blend stage for batches commercially manufactured.

REFERENCES

1. J.E. Berman, D.E. Linski, C.R. Gonzales, J.D. Hoger, P.J. Jimenz, J.A. Plarchard, R.J. Tdachac and P.F. Vogel, *J. Pharm. Sci. Tech.*, **5**, S1 (1997).
2. J. Berman and J.A. Planchard, *Drug Dev. Ind. Pharm.*, **21**, 1257 (1995).
3. J. Berman, A. Schoeneman and J.T. Shelton, *Drug Dev. Ind. Pharm.*, **22**, 112 (1996).

4. S. Bolton, Pharmaceutical Statistics: Practical and Clinical Applications, edn. 3, pp. 100-113 (1997).
5. H.G. Brittain, *Pharm. Technol.*, **26**, 67 (2002).
6. Center for Drug Evaluation and Research, 21 Code of Federal Regulations part 211.110.
7. P. Cholayudth, *J. Valid. Tech.*, **11**, 116 (2005).
8. S.C. Chow and J.P. Liu, Statistical Design and Analysis in Pharmaceutical Science: Validation, Process Controls, Practical and Clinical Applications, edn. 3, pp. 113-116 (1995).
9. G.J. Mergen, *J. Valid. Tech.*, **7**, 102 (2001).
10. Draft Guidance for Industry: Powder Blends and Finished Dosage Units-Stratified in Process Dosage Unit Sampling and Assessment, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, October (2003).
11. Draft Guidance for Industry ANDAs: Blend Uniformity Analysis, August (1999).
12. Guide to Inspection of Oral Solid Dosage Forms pre/post Approval for Development and Validation, FDA Division, January (1994).
13. C. Madsen, Statistical Methods for Assessment of Blend Homogeneity, Ph.D. Thesis from IMM, p. 24 (2002).
14. H. Saranadasa, *Pharm. Technol.*, **27**, 50 (2003).
15. United States Pharmacopoeia: USP 24/NF 19, General chapter <905> Uniformity of Dosage Units, edn. 2, pp. 2000-2001 (2000).

(*Received*: 13 December 2006; *Accepted*: 22 October 2007) AJC-6036