Chapter-10

Content Uniformity

10.1 Introduction

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. Any failure to comply with content uniformity will lead to either over dosage or under dosage, both of which are highly undesirable for obvious reasons. 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). The general problems associated with content uniformity testing is inability to detect batches where loss of homogeneity has occurred up until the testing of the finished product and the lack of any information concerning the point of failure or the mechanism by which content uniformity has been lost. However, this test is useful for assessing the consistency of:

- Powder blends before filling or compressing
- Semi-solid and liquid bulk batches before filling
- Filling during manufacturing (such as powders into capsules or liquids into vials or bottles)
- Active content within individual units post-manufacturing (such as individual tablets after compression)

Content uniformity testing involves using a content/potency assay to determine the content of active material contained in multiple different samples collected throughout the batch Examples of sample sets that may be collected for content uniformity determinations are:

- Tablets from the beginning, middle and end of a compression run
- Aliquots of bulk material taken from the top, middle and bottom of a vessel before filling
- Randomly selected bottles filled with a liquid taken out of a packaged case
- Randomly selected capsules taken from a single bottle representing 10% of the number of capsules filled into the bottle

The three main factors which can contribute to non-content uniformity problems in unit dosage forms include:

- Non-uniform distribution of the drug substance throughout the powder mix, which in turn may be attributed to the following:
  - Difference in density of drugs and excipients
  - Difference in particle size distribution of the drug and excipient
  - Improper selection of mixer
  - Inadequate mixing
  - Agglomeration
  - Development of static charge
- Segregation of the powder mix during various manufacturing processes
- Weight variation

Content uniformity of USP test is designed to establish the homogeneity of a batch. Ten unit solid dosage forms are assayed individually after which arithmetic mean and relative standard deviation is calculated. USP criteria are met if the content uniformity lies within 85-115 % of the label claim and RSD in not greater than 6 %. Provision is included in the compendium for additional testing if one or more than one unit fail to meet the standard. To assure uniform potency in the unit dose formulations of low dose drugs selected for the present study, each urea co-inclusion compounds of all the five drugs (AH, EM, GLP, IsoT and NRD) were subjected to content uniformity testing as per the following details.

10.2 Content uniformity of urea inclusion compounds

All the urea inclusion compounds containing varying proportion of drug and RAE wee subjected to content uniformity testing as per the following details

10.2.1 Content uniformity of AHIC

10.2.1.1 Method

Accurately weighed amounts of ten randomly drawn samples of AH-RAE-urea co-inclusion compounds containing the equivalent of 20mg of the drug were dissolved in 0.1 N HCl, suitably diluted to contain a concentration of ~ 10 µg/ml. Absorbance of the resulting solutions were noted at 363 nm and the percentage of drug contents in each sample was determined. The results are compiled in **Table 10.1**.

10.2.1.2 Result and discussion

The content variation among various samples of inclusion compounds was found to range from 95.9 to 99.7% of the claimed amount of drug (**Table 10.1**). The SD value observed for all the inclusion compounds containing varying proportion of drug and RAE was observed to be quite minimal. Therefore co-inclusion compounds of drug in a urea lattice exhibit high content uniformity and hence can be exploited for the development of a quality formulation.

Table 10.1 Content uniformity for different urea co-inclusion compounds of amiloride hydrochloride containing varying proportion of RAE and drug.

Sample No.	AHIC-1	AHIC-2	AHIC-3	AHIC-4	AHIC-5	AHIC-6
1	99.3	97.2	99.4	95.9	96.9	97.7
2	98.9	98.4	98.3	96.9	96.9	99.2
3	99.6	98.1	97.9	96.7	97.4	97.5
4	98.9	97.6	99.3	96.2	96.7	97.8
5	99.5	97.5	98.7	97.1	97.4	98.4
6	99.3	97.9	98.4	95.8	97.5	97.6
7	99.5	98.6	97.8	96.9	96.8	98.6
8	99.8	98.6	99.2	95.7	96.6	98.7
9	98.9	97.9	98.9	96.8	97.3	97.6
10	99.2	97.4	97.8	95.9	97.2	99.3
Mean	99.39	97.89	98.6	96.41	97.1	98.2
S.D.	± 0.338	± 0.501	± 0.623	± 0.541	± 0.328	± 0.689

10.2.2 Content uniformity of EMIC

10.2.2.1 Method

Content uniformity test was conducted on ten randomly drawn samples form all the EMIC inclusion compounds. Exactly weighed amounts of the adducts containing equivalent of 20 mg of the drug were dissolved in pH 2.2 phosphate buffer solution to contain a concentration of 0.2 mg of enalapril maleate per ml. The drug contents were

determined the HPLC method for content analysis. The results are summarized in **Table 10.2.**

10.2.2.2 Result and discussion

The contents uniformity data for different EMIC inclusion compounds containing varying proportions of RAE: drug reveals that the mean drug content for different inclusion compounds is not significantly different.

Table 10.2 Content uniformity for different urea co-inclusion compounds of enalapril maleate containing varying proportion of RAE and drug.

Sample No.	EMIC-1	EMIC-2	EMIC-3	EMIC-4	EMIC-5
1	96.9	97.6	95.6	98.1	96.8
2	97.2	98.7	95.4	98.5	96.9
3	96.4	99.1	96.2	98.9	96.1
4	96.9	98.4	96.1	97.9	96.8
5	97.8	98.9	95.3	98.5	96.3
6	97.5	98.7	96.1	97.9	96.8
7	97.1	97.6	96	98.2	95.9
8	97.7	97.1	95.4	99	96.9
9	98.1	98.6	95.4	98.8	96.1
10	97.9	96.9	95.9	98.9	96.4
Mean	97.3	98.1	95.7	98.5	96.5
S.D.	± 0.540	± 0.791	± 0.355	± 0.425	± 0.383

10.2.3 Content uniformity of GLPIC

10.2.3.1 Method

For the purpose of content uniformity determinations, exactly weighed amounts of ten randomly drawn samples of all GLP-RAE-urea co-inclusion compounds containing equivalent of 5 mg of the drug were dissolved in phosphate buffer (pH 7.4) and suitably diluted. The drug contents were determined at 276 nm spectrophotometrically. The results are compiled in **Table 10.3.**

10.2.3.2 Result and discussion

The contents of GLP in various urea co-inclusion compounds containing varying proportions of drug and RAE were found to vary from 96.1 to 99.2% of the claimed amount of drug (**Table 10.3**). The insignificant values of SD in each case reveal that co-inclusion compounds of drug in urea lattice exhibit good content uniformity and hence can be exploited for the development of a quality formulation.

Table 10.3 Content uniformity for different urea co-inclusion compounds of glipizide containing varying proportion of RAE and drug.

Sample No.	GLPIC-1	GLPIC-2	GLPIC-3	GLPIC-4	GLPIC-5
1	98.1	98.2	95.9	96.9	96.5
2	97.6	99.4	96.9	95.7	97.3
3	98	99.2	96.8	97.5	96.4
4	96.9	97.6	96.1	96.8	96.6
5	97.6	99.3	95.9	97.8	96.3
6	98.1	98.1	96.6	96.8	97.5
7	96.6	97.8	96.8	97.1	96.5
8	97.6	97.4	96.1	96.9	97.3
9	96.8	99.3	96.5	98.1	96.5
10	97.1	99.4	96.4	97.2	97.1
Mean	97.4	98.6	96.4	97.2	96.8
S.D.	±0.557	±0.824	±0.380	±0.661	±0.447

10.2.4 Content uniformity of UIOA

10.2.4.1 Method

Exactly weighed amounts of all *cis*-RA-urea co-inclusion compounds containing equivalent of 20 mg of the drug were dissolved in methanol. The solutions were suitably diluted to contain a concentration of 10 µg/ml of the drug. The drug content was determined by HPLC method. The results are summarized in **Table 10.4**.

10.2.4.2 Result and Discussion

Table 10.4 shows that the content of *cis*-RA in urea co-inclusion compounds with different ratio of drug: RAE was not significantly different from the claimed amount of drug. The value of SD was also found to be insignificant for all the urea co-inclusion compounds containing varying proportions of drug and RAE.

Table 10.4 Content uniformity for different urea co-inclusion compounds of *cis*-RA containing varying proportion of RAE and drug.

Sample No.	UIOA-1	UIOA-2	UIOA-3	UIOA-4	UIOA-5
1	96.4	99.7	98.9	94.1	97.1
2	94.4	97.5	100.4	95.6	99.1
3	94.6	98.8	99.6	94.3	97.2
4	95.7	100.4	98.4	94.5	98.9
5	95.9	97.8	97.4	95.4	96.4
6	96.1	98.7	98.7	96.1	96.6
7	94.7	100.1	100.2	94.1	97.8
8	94.3	99.6	98.7	95.5	97.3
9	96.1	99.5	98.5	94.9	98.4
10	95.8	99.4	98.3	93.9	96.2
Mean	95.4	99.1	98.9	94.8	97.5
S.D.	±0.804	±0.949	±0.914	±0.769	±1.047

10.2.5 Content uniformity of NRDIC

10.2.5.1 Method

Ten samples containing equivalent of 40 mg of drug were drawn randomly from different urea co-inclusion compounds containing varying proportion of NRD and RAE. The samples dissolved in water and suitable diluted to contain 20 µg/ml of the drug. The concentration of NRD in each solution was determined spectrophotometrically at 272 nm. The results are compiled in **Table 10.5.**

10.2.5.2 Result and discussion

Various urea co-inclusion compounds containing varying proportions of NRD and RAE were observed to contain drug within concentration range of 97.9 % to 100.8 % of the claimed amount of drug. Quite minimal values of SD demonstrate good content uniformity among different samples of urea co-inclusion compounds.

Table 10.5 Content uniformity for different urea co-inclusion compounds of nicorandil containing varying proportion of RAE and drug.

Sample No.	NRDIC-1	NRDIC-2	NRDIC-3	NRDIC-4	NRDIC-5
1	98.7	99.1	99.6	98.4	99.1
2	98.1	100.6	99.7	99.3	100.5
3	99.5	99.9	100.4	98.5	98.8
4	100.1	97.8	101.7	99.6	99.4
5	98.2	100.5	99.9	98.3	98.7
6	97.2	99.4	100.4	98.8	100.4
7	99.1	98.7	99.9	99.3	100.2
8	100.4	100.1	99.7	98.2	99.6
9	97.9	100.5	100.2	98.6	99.4
10	99.7	99.7	100.8	99.1	100.5
Mean	98.9	99.6	100.2	98.8	99.7
S.D.	±1.043	±0.932	±0.657	±0.486	±0.793

10.3 Conclusion

Retrofit analysis of data in **Table 10.1 to 10.5** reveals good content uniformity for all the co-inclusion compounds of urea with various drugs studied in the present investigations. Thus, co-inclusion of drug in urea lattice appears applicable to development of formulation with high content uniformity and hence can be exploited for the development of a quality formulation.