International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 5, May 2026 ijppr.humanjournals.com ISSN: 2349-7203

A Review of the Formulation and Evaluation of Low-Dose Hydrochlorothiazide Tablets with Improved Blend Uniformity

Asaithambi.R*, Dr.Kamalakkannan Venkatachalam, Dr.Sangameswaran Balakrishnan, Dr.Parthiban Ganeshan.

Department of Pharmaceutics, SSM College of Pharmacy, Erode, Tamil Nadu, India

Received: 27 March 2026 Revised: 22 April 2026 Accepted: 28 April 2026

ABSTRACT

Because a small number of API particles per unit dose increases the effects of segregation, agglomeration, sampling bias, and process disruptions, low-dose solid oral dosage forms are susceptible to blend non-uniformity (BU) and content non-uniformity (CU). Hydrochlorothiazide (HCTZ) tablets, which are typically sold at 12.5 mg, are an example of a typical low-dose situation where production must ensure mixing adequacy as a CGMP expectation and CU testing is typically required under pharmacopeial rules. HCTZ is defined as a crystalline powder that is somewhat soluble in water. It is frequently made by granulation or direct compression using excipients chosen for flow, lubrication, wetting/disintegration, and compressibility. [2, 4] The physicochemical characteristics of HCTZ that are pertinent to uniformity issues are covered in this review, along with the mechanisms by which powder blends separate during manufacturing, practical formulation and process strategies to improve blend uniformity, such as ordered mixing, granulation techniques, particle engineering, and process analytical technology (PAT) with near-infrared (NIR) spectroscopy, as well as evaluation methods compliant with USP <905>, USP <1097," and 21 CFR 211.110. [1,5,3,6,7]

Keywords: hydrochlorothiazide; low-dose tablets; blend uniformity; content uniformity; segregation; direct compression; wet granulation; PAT; near-infrared spectroscopy; USP <905>

1. INTRODUCTION

Because each tablet should contain the medicinal material within a specific range around the label claim, uniformity of dosage units is a crucial quality trait. USP (905) The standardised foundation for proving uniformity using an Acceptance Value (AV) method is provided by Uniformity of Dosage Units, mainly through Content Uniformity for low-dose medicines. [1] Blend consistency and process control are crucial for low-dose tablets since any drug segregation during blending, material movement, or tablet pressing might result in significant variance in potency. (1, 8)

Commercial pills containing 12.5 mg, 25 mg, and 50 mg of HCTZ are available. According to the official medication label, it is a white, crystalline powder with very little water solubility. Microcrystalline cellulose (MCC), pregelatinized starch, colloidal silicon dioxide, magnesium stearate, and sodium lauryl sulphate (SLS) are common excipients found in marketed HCTZ formulations. These excipients represent typical requirements for powder flow, tablet hardness, lubrication, and drug wetting. [2]

Blend uniformity evaluation is a statutory GMP requirement since 21 CFR 211.110 mandates that producers have documented in-process controls, including confirmation that mixing is enough to provide batch consistency. [3] Science-driven approaches to pharmaceutical manufacture are also supported by the FDA's PAT recommendation, which promotes the use of real-time measurements and controls, such as in-line NIR spectroscopy, to monitor blend consistency. [6]

2. Hydrochlorothiazide: Properties Relevant to Low-Dose Tablet Uniformity

The physical and chemical properties of HCTZ have a direct impact on how well it can be produced into consistent tablets. According to published data, HCTZ has poor solubility in water but higher solubility in alkaline conditions, low lipophilicity (XlogP about −0.1), and acid dissociation constants (pKa) close to 7.9 and 9.2. [4,2] In order to guarantee consistent drug distribution and sufficient drug release at a low dose, these features make careful excipient selection and strict process control even more crucial. [2, 8]

Table 1. HCTZ attributes and implications for blend/content uniformity

Attribute	Evidence	Implication for low-dose tablets
Common marketed strength	12.5,25,50 mg tablets [2]	12.5 mg is a modest dose; under USP <905>, CU testing usually applies. [1,2]
Solid state	White crystalline powder in the solid form [2]	Agglomeration and particle size distribution (PSD) have a significant impact on CU at low dosage. [8,9]
Solubility	Slightly soluble in water; more soluble in alkaline media [2,4].	requires a strong disintegration/wetting design; performance may be subject to excipient variability; [2,10]
pKa	~7.9 and 9.2 [4]	pH-dependent behaviour influences icroenvironmental pH impacts and dissolution design. [4,2]
Typically, excipients	Common excipients include MCC, pregelatinized starch, colloidal silica, magnesium stearate, and SLS [2].	This suggests a typical DC strategy with flow assistance, lubrication, and wetting augmentation. [2, 8].

3. Mechanistic Causes of Blend Non-Uniformity in Low-Dose Tablets

3.1 Segregation mechanisms

Powder combinations can re-separate during handling, even after being thoroughly blended. In the production of tablets, this occurs primarily through three processes: rolling or trajectory separation (particles moving differently due to size or density differences), fluidisation or air entrainment (lighter particles becoming airborne), and sifting or percolation (smaller particles falling through gaps between larger ones). Particle size, density, and powder flow behaviour variations during transfer and hopper discharge amplify these impacts. [8,11].

3.2 Low-dose amplification and API particle statistics

The quantity and size of API particles play a major role in the homogeneity of each tablet when the dose is relatively low. Tight control over particle size distribution (PSD) is crucial at low dosages since research has shown that even one large API particle can produce a tablet with a dangerously high drug concentration. [9]

3.3 Sampling bias

It is challenging to obtain a properly representative sample from a powder blend, particularly when the blend is not exactly homogeneous. According to USP <1097>, biased sampling might result in entirely incorrect conclusions about blend quality because sampling is by its very nature an estimation procedure. Therefore, sampling plans need to be carefully crafted to maintain the integrity of the sample while still being representative. (5)

Table 2. Common BU/CU failure Patterns

Observed issue	Likely causes	Typical stage	Key sources
High tablet-to-tablet variability	Low particle count per unit; coarse/wide API PSD; agglomeration	Any stage; amplified by low dose	[1,8,9]
Potency drift during compression	Drug segregation in hopper/feed frame transfer-induced de mixing	Transfer → hopper → feed frame	[8]
High location-to-location blend variability	Inadequate macro-mixing; sampling bias	Blender / IBC / bin	[3,5]
Acceptable CU but variable dissolution	Excipient variability (e.g., disintegrant differences); incorporation method	Formulation /granulation	[10]

4. Formulation Strategies to Improve Blend Uniformity

4.1 Direct compression (DC): excipient selection and ordered mixing

The easiest method of production is direct compression, which keeps the medication out of the heat and moisture. However, it poses significant difficulties for low-dose products in terms of sensitivity to lubricant levels, mixing homogeneity, and segregation danger. In order to achieve an equitable initial distribution and avoid concentration hotspots, formulators use geometric dilution to gradually blend the API into progressively greater quantities of excipient [12,8]. [12,8] These DC requirements are met by the standard HCTZ excipient package (MCC, starch, silica, magnesium stearate, SLS).[2]

4.2 Wet granulation (WG): immobilization and robustness

By physically containing the API within granules, wet granulation improves the blend's flow and compressibility while decreasing the API's propensity to separate during subsequent handling. But it complicates the process and exposes the medication to heat and moisture. [12, 8] The source of the super disintegrant crospovidone and how it was added to the formulation had a substantial impact on drug release, according to a recent study on HCTZ tablets. Specifically, adding it outside the granule (extra-granular) generated better dissolving than incorporating it within the granule.[10]

4.3 Dry granulation / roller compaction

Without water, dry granulation can lessen segregation and enhance blend flow. More generally, research on low-dose tablets demonstrates that formulation composition and manufacturing selection can affect CU at scale. [13, 8]

4.4 Particle engineering / API-carrier composites

Highly uniform drug distribution in low-dose direct compression products is made possible by sophisticated particle engineering approaches, such as loading the API onto porous carrier particles, which can change the API's physical behaviour to closely resemble that of the carrier. Many of the variability problems associated with PSD are eliminated by this method, but it necessitates further processing and careful characterisation. [14, 9]

Table 3. Formulation approaches to improve BU in low-dose HCTZ tablets

Strategy	Principle	Expected benefit	Practical cautions	Key sources
1. Ordered mixing/carrier preblend	Promote API adhesion to carrier (e.g., MCC)	Improved micro-distribution; reduced segregation	Depends on API–excipient surface interactions	[8,9,12]
2. DC with functional excipients (flow/wetting)	Use silica/SLS, optimized lubricant addition	3. Better flow Consistency and wetting	Over-lubrication can worsen flow/segregation	[2,12]
Wet granulation	4. Immobilize API in granules	Lower segregation; improved flow	5. Moisture exposure; disintegrant placement critical	[12,10]
6. Dry granulation /roller compaction	7. Densify blend without water	8. Potential CU improvement	9. Ribbon/milling non-uniformity risk	10. [13]
11. Particle engineering composite	12. API-carrier composite dictates powder 13. properties	14. Highly robust CU at very low dose	15. Requires added DS processing & characterization	16. [14,9]

5. Process Strategies to Improve Blend Uniformity

5.1 CGMP and process control requirements

Manufacturers are required by 21 CFR 211.110 to establish and record in-process processes that include checking if blending is adequate to provide homogeneity and consistency. Every manufacturer must have a well-defined blend uniformity control strategy with statistically valid, scientifically supported criteria as a result of this regulatory obligation. [3]

5.2 Designing out segregation during transfer and feeding

Drug segregation frequently happens during die loading, hopper discharge, and the transfer of the blend from the blender to the tablet press. A crucial factor is equipment design; for instance, mass flow hoppers, in which all material moves uniformly, are better than funnel flow systems, in which the core material flows first [8]. Minimising the height from which powder falls, regulating air displacement with appropriate venting, and selecting feeder and hopper layouts that eliminate favoured powder flow pathways are all practical ways to lessen segregation. [8,11]

5.3 Risk-based BU/CU approaches and lifecycle thinking

Applying risk-based thinking to blend and content uniformity management across the whole product lifecycle—from original process design to manufacturing certification to continuous production monitoring—is advised in a position paper published by the IQ Consortium. This method minimises the requirement for excessive, invasive sampling while aligning uniformity assurance with real process knowledge. [7]

6. Evaluation of Low-Dose HCTZ Tablets

6.1 Blend evaluation (pre-compression)

Particle size distribution, bulk and tapped density, powder flow, moisture/loss on drying (LOD), and drug concentration should all be evaluated at various points inside the blender or container prior to tablet compression. Designing sample strategies that reduce bias and give an accurate image of blend homogeneity is guided by USP <1097>. [5].

6.2 Dosage unit uniformity (post-compression): USP <905>

Following compression, tablets are assessed using the USP <905 frame work, which determines an Acceptance Value (AV) based on 10 tablets in Stage 1, with a Stage 2 option if preliminary results are ambiguous. HCTZ 12.5 mg tablets must be examined using Content Uniformity (CU) rather than Weight Variation (WV) since they contain less than 25 mg of medication. [1,2]

6.3 PAT/NIR for real-time monitoring

The regulatory basis for utilising real-time analytical techniques in manufacturing is provided by the FDA's PAT guidance. [6] In-line NIR spectroscopy has been effectively used in practice to monitor mix uniformity directly in the tablet feed frame, enabling real-time variability identification and prompt remedial action. [15]

Table 4. Evaluation tests supporting BU/CU assurance from blend to tablet

Stage	Test	Purpose	Frame work/ expected	Key sources
Blend	Representative sampling plan	Avoid based conclusions	USP <1097 principles	[5]
Blend	Blend assay across locations	17. Detect macro-non uniformity	Supports mixing adequacy expectation	[3,5]
Tablet	Content Uniformity (AV)	Confirm unit dose uniformity	USP <905 staged AV criteria	[1]
Tablet	WV applicability check	Determine if WV is allowed	18. USP<905 ≥25 mg And ≥25% rule	[6,15]
19. Performance	20. Disintegration/ dissolution	21. Ensure consistent release	22. Sensitive to excipient Source & method	[10,2]

7. Conclusions

spanning three areas: process engineering (minimising segregation during powder transfer and tablet press feeding), formulation design (using ordered mixing, suitable excipient selection, granulation, or particle engineering), and material controls (particularly controlling API particle size). [8, 9, 12] Both final tablet uniformity approval under USP <905° and in-process mixing assurance under GMP regulations are required by regulatory and pharmacopeial systems. PAT tools, such as NIR spectroscopy, can assist continuous lifecycle quality control and offer real-time uniformity monitoring when appropriately verified. [3,1,6,15]

REFERENCES

1. United States Pharmacopeial Convention. **<905> Uniformity of Dosage Units**. Rockville (MD): USP; 2023.
2. U.S. Food and Drug Administration. **Hydrochlorothiazide tablets, USP (12.5 mg, 25 mg, 50 mg): prescribing information**. Silver Spring (MD): FDA; 2011.
3. Electronic Code of Federal Regulations. **21 CFR 211.110 Sampling and testing of in-process materials and drug products**. Washington (DC): U.S. Government Publishing Office; updated 2026. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211/subpart-F/section-211.110
4. National Center for Biotechnology Information. **PubChem Compound Summary: Hydrochlorothiazide (CID 3639)**. Bethesda (MD): National Library of Medicine; updated 2026. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Hydrochlorothiazide
5. United States Pharmacopeial Convention. **<1097> Bulk Powder Sampling Procedures**. USP–NF. Rockville (MD): USP; 2023.
6. U.S. Food and Drug Administration. **PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance**. Guidance for Industry. Rockville (MD): FDA; 2004. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pat- framework-innovative-pharmaceutical-development-manufacturing-and-quality- assurance
7. Bautista M, Caille S, Corredor C, et al. Blend uniformity and content uniformity in oral solid dosage manufacturing: an IQ Consortium industry position paper. **AAPS J**. 2025;27:49. doi:10.1208/s12248-025-01028-7.
8. Jakubowska E, Ciepluch N. Blend segregation in tablets manufacturing and its effect on drug content uniformity—A review. **Pharmaceutics**. 2021;13(11):1909. doi:10.3390/pharmaceutics13111909.
9. Rohrs BR, Amidon GE, Meury RH, Secreast PJ, King HM, Skoug CJ. Particle size limits to meet USP content uniformity criteria for tablets and capsules. **J Pharm Sci**. 2006;95(5):1049–1059. doi:10.1002/jps.20587.
10. Yavari A, Sadjady SK, Moniri E, Nokhodchi A, Haghighat Talab F. Investigating the influence of crospovidone's manufacturer variability on dissolution profiles of hydrochlorothiazide tablets. **AAPS PharmSciTech**. 2025 Feb 4. doi:10.1208/s12249- 025-03039-1.
11. Prescott J, Carson J. Analyzing and overcoming industrial blending and segregation problems. In: Rosato AD, Blackmore DL, editors. **IUTAM Symposium on Segregation in Granular Flows**. Dordrecht: Springer; 2000. p. 89–101.
12. Jovanovikj F, Miovska I, Popovska Jakimovska V, et al. Approaches for optimization of formulation and manufacturing process of low-dose tablets. **Maced Pharm Bull**. 2022;68(Suppl 1):241–242.
13. Morris DG, Truitt BF, Kong A, Leyva N, Luner PE. Influence of formulation composition and processing on the content uniformity of low-dose tablets manufactured at kilogram scale. **Pharm Dev Technol**. 2009;14(5):451–460.
14. Sun WJ, Aburub A, Sun CC. Particle engineering for enabling a formulation platform suitable for manufacturing low-dose tablets by direct compression. **J Pharm Sci**. 2017;106(7):1772–1777.
15. Li Y, Anderson CA, Drennen JK 3rd, Airiau C, Igne B. Development of an in-line near-infrared method for blend content uniformity assessment in a tablet feed frame. **Appl Spectrosc**. 2019;73(9):1028–1040. doi:10.1177/0003702819842189.

How to cite this article:
Asaithambi.R et al. Ijppr.Human, 2026; Vol. 32 (5):197-201.
Conflict of Interest Statement: All authors have nothing else to disclose.