Effect of Drug Particle Size on Blend Segregation and Content Uniformity of Low Dose Tablets

Zahra N. Mahmoudi, Thomas Farrell, Sampada B. Upadhye, and Ali R. Rajabi-Siahboomi

Poster Reprint
Starch 1500®

Purpose

Micronized drugs may have a tendency to segregate in blends due to their increased surface area and agglomeration. [1,2] To reduce their high surface energy, microparticles aggregate and form larger particles that could cause issues in blending.[3,4] Segregation, which is de-mixing of a blend, will result in poor content and weight uniformity as well as variation in dissolution, appearance, taste and stability of final solid dosage forms. Segregation is equipment and material dependent.

The choice of filler for a low dose blend of micronized drugs could be critical to ensure good dispersability and uniformity of a micronized drug throughout the blend with no segregation. Previous studies have indicated that Starch 1500®, partially pregelatinized maize starch and microcrystalline cellulose (MCC) mixtures provided excellent blend uniformity, with good compaction and disintegration properties. [5, 6]

In this study, a combination of Starch 1500 and MCC was selected as the filler. One of the objectives was to evaluate the effect of drug particle size on blend segregation of low dose formulations of micronized hydrochlorothiazide (HCTZ), a slightly water soluble model drug. The other objective was to study the effect of drug particle size and drug load on dissolution rate of micronized drug tablets; two concentrations, 1% and 10% of the micronized drug, were used in these studies.

Methods

Composition and Preparation of Blends

HCTZ is a crystalline powder with slight solubility in water (0.7 mg/ml). HCTZ crystals were micronized in order to achieve three size fractions (Micron Technologies, Malvern PA). Particle size analysis was performed using a Malvern Mastersizer 2000 equipped with a Scirocco 2000 dry dispersion unit. The sample container was inverted and mixed several times to ensure a homogenous mixture for sampling. Approximately one gram of sample was distributed evenly along the vibratory feeder of the equipment for transferring to the measuring unit. Three 10 second runs were performed per sample, and an average of the three particle size distributions was calculated. The non-micronized and each micronized particle size fraction of HCTZ were used to prepare formulations with compositions shown in **Table 1**. The micronized HCTZ fractions were delumped by passing through a Comil equipped with a 1 mm grater screen at 2500 rpm speed.

Preparation and Testing of 1% HCTZ Blends

To study the effect of particle size on segregation/dissolution of low dose tablets, four similar formulations containing 1:1 ratio of partially pregelatinized starch (Starch 1500, Colorcon): Microcrystalline cellulose NF (MCC, Microcel 102, Blanver) as filler, 1% HCTZ with different particle sizes and 0.5% magnesium stearate (Hyqual, Mallinckrodt), were prepared. All ingredients were weighed to make a 10 kg batch. MCC was loaded in a low shear 32 quart V blender, followed by HCTZ and Starch 1500.

Table 1. Blend Composition

Ingredients	1% Drug Load W/W (%)
Hydrochlorothiazide *	1
Pregelatinized starch NF	49.25
Microcrystalline cellulose NF	49.25
Magnesium stearate	0.5
Total	100

*Four fractions of HCTZ with different PSD.
Each batch consisted of one fraction of HCTZ.

Each mix was blended up to 60 min and samples for blend uniformity (BU) testing taken, in duplicate, from 18 predefined locations in the blender: top, centre and bottom; and on the left and right side of the blender using a powder sample thief at 5, 10, 20, 30 and 60 min blend time. Powder sample size was 250 mg to 750 mg, equal to 1 to 3 times the tablet target weight. Samples were assayed individually, and results were used to calculate the arithmetic mean and relative standard deviation (RSD). Blends were considered uniform if the mean value was within the range of ±10% of the target potency, and the RSD value was less than 5% (FDA draft guidance).[7]

Compression and Physical Testing of 1% HCTZ (2.5 mg dose, 1% drug load) Tablets

Magnesium stearate (sieved through a 60 mesh screen) was added to each mix. Mixes were blended for three min, and each blend compressed into 250 mg tablets on an instrumented (SMI) Piccola (Riva) rotary tablet press, using four sets of 5/16" (7.94 mm) standard round concave tooling. Samples of tablets from the beginning, middle and end of a 70 min run were evaluated for weight variation and content uniformity (CU). Tablets (n=10) were assayed individually, and the results used to calculate the arithmetic mean and the RSD. Tablets were considered uniform if the mean value was within the range of ±15% of the target potency and the RSD was less than 6%.

Preparation and Physical Testing of 10% HCTZ (25 mg dose, 10% drug load) Tablets

To study the effect of particle size/drug load on dissolution, four similar formulations consisting of 1:1 and 1:2 ratios of Starch 1500:MCC and 10% HCTZ, only differing in drug particle size, were prepared to make a 200 g batch. MCC was loaded in a low shear 2 quart V blender followed by drug and Starch 1500. The mixture was blended for 5 min. Colloidal silicon dioxide (Cab-O-Sil M-5P, Cabot) and a small portion of the mixture were passed through a 40 mesh screen to delump, and then blended for 2 min. Pre-sieved magnesium stearate was added to each mixture and blended for 3 min. Tablets were prepared as described above, using one set of the tooling. The physical properties of the compressed tablets were evaluated for thickness, weight and crushing strength on an Erweka Multicheck automatic tablet tester. The tablet disintegration time (DT) was determined on an Erweka ZT 44 disintegration apparatus using deionized water.

Dissolution Testing

The dissolution method, shown in **Table 2**, was used to test the tablets (n=6), with analysis by UV/VIS through a 0.5 cm cell @ 272 nm.

Table 2. Dissolution Method

USP Apparatus	Speed (RPM)	Medium	Volume (mL)	Sampling Times (minute)
I (Basket)	100	0.1 N HCl	900	5, 10, 15, 30, 45, 60

Results

Particle size distributions (PSD) of hydrochlorothiazide before and after micronization are shown in **Table 3**.

Table 3. Particle Size Distribution of Hydrochlorothiazide

ID	D (v, 0.1)	D (v, 0.5)	D (v, 0.9)	D [4,3]
Non-micronized, NonM (µm)	16.9	119.0	321.0	146.9
Micronized, M1 (µm)	5.9	29.2	136.3	54.6
Micronized, M2 (µm)	4.4	14.8	46.4	23.0
Micronized, M3 (µm)	3.1	9.9	26.6	12.8

D [4, 3] is the volume mean particle diameter.

Blend Uniformity of 1% Blends

Homogeneity of 1% HCTZ blends is shown in **Table 4**. The average potency assay of 91.5% and a low RSD of 3.4% met the specification for BU of HCTZ 13 µm at 20 min blend time. Further blending slightly improved the uniformity (lower RSD values) with no segregation at 60 min.

Table 4. Blend Uniformity of the Formulations Consisted of Non-Micronized and Micronized HCTZ

Blend Time (min)	Non-Micronized, NonM (mean 147 µm)		Micronized M1 (mean 55 µm)		Micronized M2 (mean 23 µm)		Micronized M3 (mean 13 µm)	
	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)
5	94.9	3.1	95.1	3.7	91.6	3.6	88.7	7.8
10	94.1	3.8	91.9	1.8	94.5	10.2	97.2	5.4
20	94.9	4.0	93.3	1.9	92.7	3.4	91.5	3.4
30	96.7	3.3	93.9	1.7	94.4	2.0	91.8	2.5
60	96.5	3.6	93.3	1.7	93.4	2.7	93.8	1.2

Similarly, blend homogeneity for HCTZ 23 µm was achieved in 20 min with RSD value of 3.4% (92.7% average assay) with no segregation at 60 min blend time. Both micronized HCTZ 55 µm and non-micronized HCTZ 147 µm blends were uniform at 5 min blend time with RSD value of 3.7% (95.1% average assay) and 3.1% (94.9% average assay), respectively. It was demonstrated that to achieve uniformity with consistently low RSD, longer blend times were required as PS decreased. Since no segregation in any HCTZ blends was observed, it indicates that a combination of Starch 1500 and MCC successfully disperses APIs with a wide range of particle sizes in low dose formulations. It has been reported that irregular surfaces of Starch 1500 particles are suitable for micronized drug adsorption, rendering content uniformity of a formulation with low dose drug. [8, 9]

Content Uniformity and Weight Variations of 1% HCTZ Tablets

Figure 1 shows the average tablet weights as a function of compression time. Tablets weight variations were low, which indicated a consistent tablet weight throughout the compression run.

Figure 1. Weight Variation of Tablets Comprising 1% HCTZ (n=10)

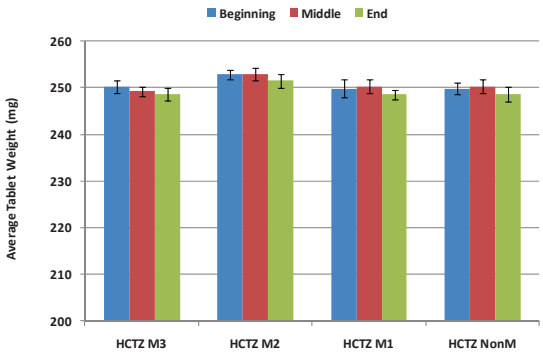


Table 5. Content Uniformity of Tablets Comprising 1% HCTZ (n=10)

Formulation ID	Beginning		Middle		End	
	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)
NonM (dm=147 µm)	98.2	3.6	97.8	2.3	100.5	3.2
M1 (dm=55 µm)	98.3	1.4	100.3	0.9	100.4	1.1
M2 (dm=23 µm)	98.2	0.9	97.9	1.1	98.3	0.9
M3 (dm=13 µm)	99.5	1.4	98.4	0.7	99.0	1.2

Summary results of content uniformity testing on HCTZ tablets 2.5 mg dose are shown in **Table 5**. The results indicated that all tablets had acceptable CU with RSD < 1.5% for micronized HCTZ tablets and RSD < 4% for NonM HCTZ tablets. All potency assays were within a range of 97-101% of the target and met the specifications. No segregation was seen during tableting as the RSD values, and the average assay didn't change from the beginning to the middle and the end of the run.

Properties of 10% HCTZ Tablets

Table 6 compares properties of HCTZ 25 mg dose tablet and the ejection force during tableting. Both sets of tablets have short DT, high mechanical strength, low weight variation, and low ejection forces indicating robust formulations with good flow and sufficient lubrication.

Table 6. Comparative Properties of Tablet Formulations Comprising 10% HCTZ (n=10)

HCTZ Tablets	DT (min)		Tensile Strength (MPa)		Average Tablet Weight (mg, n=10) (RSD)		Ejection Force (N)	
Starch 1500:MCC Ratio	1:1	1:2	1:1	1:2	1:1	1:2	1:1	1:2
NonM (dm=147 µm)	1.26	0.38	2.8	2.7	252.3 ±(0.42)	251.2 ±(0.34)	57	66
M1 (dm=55 µm)	0.98	0.36	3.1	2.9	252.2 ±(0.48)	251.5 ±(0.28)	55	57
M2(dm=23 µm)	0.79	0.31	3.0	2.7	250.9 ±(0.29)	250.8 ±(0.39)	41	51
M3(dm=13 µm)	1.48	0.28	3.5	2.9	251.6 ±(0.40)	252.8 ±(0.32)	46	56

Dissolution study

Dissolution profiles of 1% HCTZ tablets, consisting of 1:1 ratio of Starch 1500:MCC, are shown in **Figure 2**. Tablets containing micronized HCTZ clearly demonstrated complete dissolution and faster release rates than tablets containing non-micronized HCTZ. It was shown that a simple micronization process along with the selection of appropriate fillers such as a combination of MCC:Starch 1500 resulted in a faster release profile for slightly soluble drugs. However, further decreases in mean particle size from 55 to 13 µm did not bring about an enhancement in the dissolution rate of HCTZ from the tablets.

Figure 2. Comparative Dissolution Profiles of 1% HCTZ Tablets Containing 1:1 Ratio of Starch 1500/MCC (n=6)

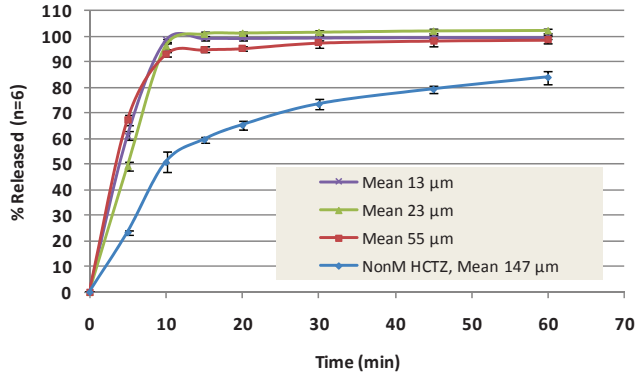


Figure 3. Comparative Dissolution Profiles of 10% HCTZ Tablets Containing 1:1 Ratio of Starch 500/MCC (n=6)

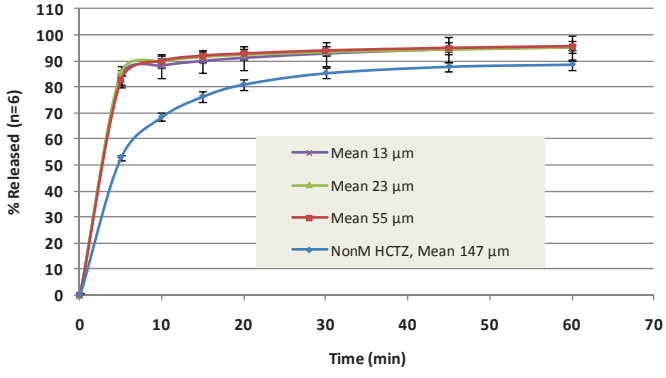
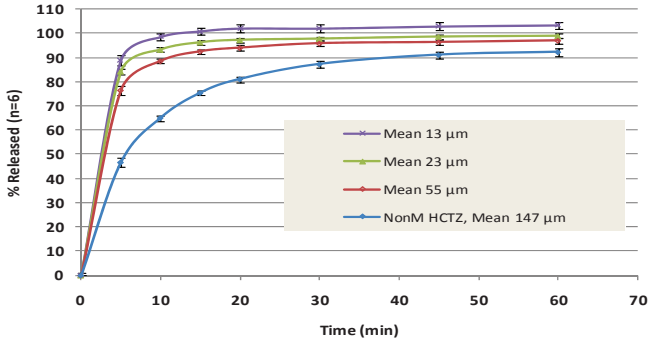


Figure 4. Comparative Dissolution Profiles of 10% HCTZ Tablets Containing 1:2 Ratio of Starch 1500/MCC (n=6)



Conclusions

Starch 1500:MCC combinations were successfully used in formulation of a low dose micronized drug, with no segregation during blending or compression processes. Acceptable blend and content uniformity of HCTZ tablets were achieved, with no de-mixing observed during extended blending and compression.

Micronization of HCTZ significantly improved the dissolution rate from tablets due to particle size reduction, and increased surface area; further particle size reduction (<55 µm) of HCTZ (M1) did not increase dissolution rate. Also the higher drug loading (10%) did not have any adverse effect on enhanced dissolution rate from micronized HCTZ tablets. This is an important finding, since itindicates a need to determine the optimized micronization limit of APIs and its possible correlation to the physic-ochemical and powder characteristics of APIs.

References

1. Zheng J. Formulation and analytical development for low-dose oral drug products. USA: John Wiley & Sons, Inc; 2009: 162, 167-170
2. McGinity J. W. et al. Dissolution and uniformity properties of ordered mixes of micronized griseofulvin and a directly compressible excipient. Drug Development and Industrial Pharmacy 1985; 11(4):891-900
3. Yalkowsky S.H. and Bolton S. Particle size and content uniformity. Pharmaceutical Research. 1990; 7(9): 962-966.
4. Zhang Y. and Johnson K.C. Effect of drug particle size on content uniformity of low-dose solid dosage forms. *Int. J. Pharm.* 1997; 154: 179-183.
5. Mahmoudi Z. N. et al. The influence of filler in blend uniformity of micronized drugs. Contributed poster, AAPS Annual Meeting (USA) 2010
6. Colorcon Technical Data. Direct compaction formulation used to produce chlorpheniramine maleate Direct Compaction, July 2003
7. FDA's Draft Guidance for Industry "Powder blends and finished dosage units - stratified in-process dosage unit sampling and assessment" October 2003
8. Kausar N. et al., Assessment of low-dose content uniformity of indomethacin in excipient blends using FT-Raman mapping spectroscopy. Contributed poster, AAPS Annual Meeting (USA) 2006
9. Ahmad H. and Shah N. Formulation of low dose medicines – Theory and Practice. *Amer. Pharm. Rev.* 2000; 3 (3): 1-5

For more information, contact your Colorcon representative or call:

North America **+1-215-699-7733**

Europe/Middle East/Africa **+44-(0)-1322-293000**

Asia Pacific **+65-6438-0318**

Latin America **+54-1-5556-7700**

You can also visit our website at **www.colorcon.com**