FACULTY OF PHARMACEUTICAL SCIENCES

LABORATORY OF PHARMACEUTICAL TECHNOLOGY

THE EFFECT OF PARTICLE SIZE ON THE SUBLIMATION OF BUTYLHYDROXYTOLUENE IN TABLETS

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1. INTRODUCTION

- An increase in the number of oxidation-sensitive APIs in recent years can require the **implementation of antioxidants in oral solid dosage forms**.
- The antioxidant butylhydroxytoluene (BHT) **sublimates at higher temperatures**, which could cause problems during processing.

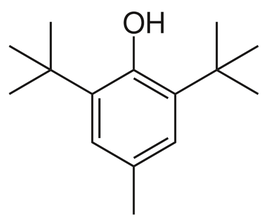

Figure 1: Structure of BHT.

2. OBJECTIVES

- Determination of the extent of BHT sublimation **in tablets**.
- Investigating the **influence of particle size** of BHT on the sublimation behaviour.

3. MATERIALS & METHODS

Fractionation of BHT

Milling & sieving

↓

Moisture content

via Karl-Fischer titration

↓

Weight loss after 1h storage

at 40, 50 and 60°C

Fraction	Particle size (µm)
1	100 – 180
2	180 – 250
3	250 – 315
4	315 – 500
5	500 – 750

Table 1: Particle size fractions isolated from coarse BHT.

Tableting

- **MedelPharm STYL'One Evo**

  → Uniaxial confined compression at 25 kN in a 11.28 mm die
- **Formulation:** 1% w/w BHT – 0.5% w/w MgSt – 98.5% w/w MCC PH-102

Sublimation in tablets

Content uniformity

via High-Performance Liquid Chromatography (HPLC)

↓

Storage

Static oven at 50°C for 5 days

↓

Visual check

X-Ray micro-computed tomography (XµCT)

BHT content via HPLC

5. CONCLUSION

- No relationship between particle size and degree of sublimation of pure BHT.
- Inclusion of BHT in a tablet did not prevent sublimation.
- **Particle size influenced the sublimation rate**. Larger particles sublimate slower, as some BHT was left in core of tablet when particle size > 250 µm.

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4. RESULTS

Sublimation of pure BHT

Moisture content:

- For all BHT size fractions <0.14%.

  → No correlation between size fraction and moisture content.

  → All weight loss during storage can be attributed to BHT sublimation.

Weight loss:

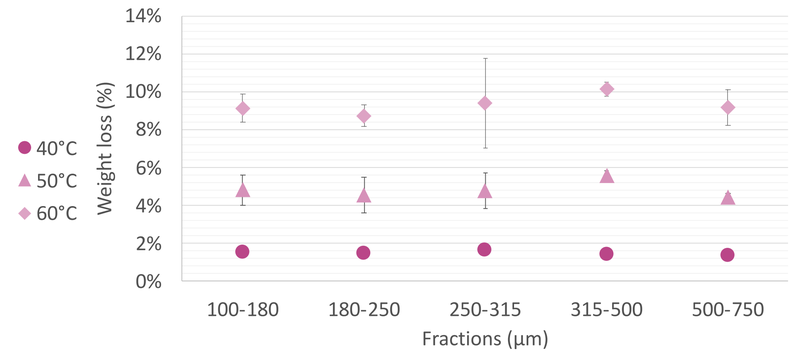


Figure 2: Weight loss of the BHT size fractions stored for 1 hour at different temperatures.

- Sublimation degree ~ temperature.
- No significant difference between size fractions of BHT.
- Partial melting at 60°C.

  (Tm BHT: 70°C)

Sublimation of BHT in tablets

Content uniformity:

- **Fraction 1-4:** 100.3 ± 7.3 %

  → good content uniformity.
- **Fraction 5:** 78.7 ± 34.0 %

  → inhomogeneous BHT distribution.
- Using larger particle size

  → Higher variability of BHT content.

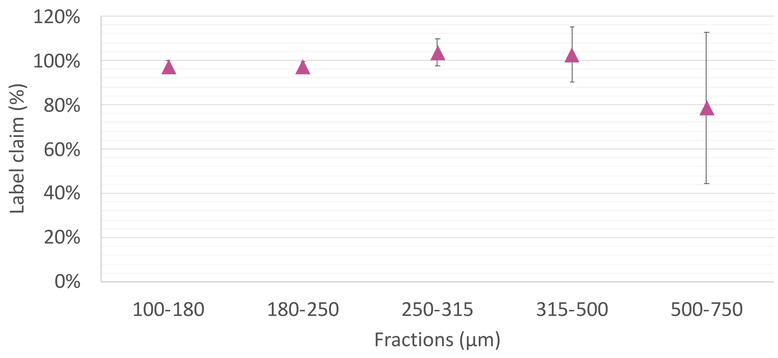


Figure 3: Content uniformity of tablets prepared with each size fraction of BHT.

Sublimation degree:

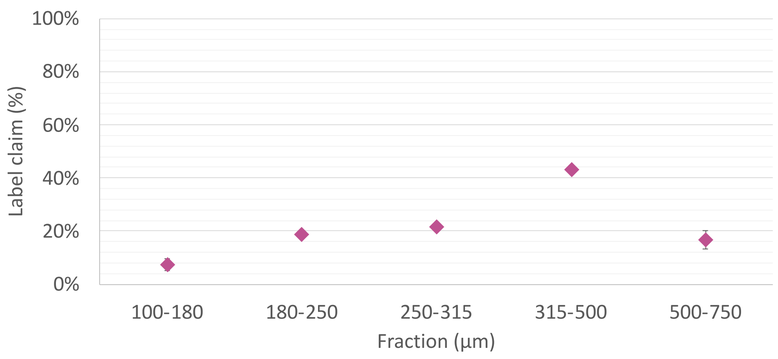


Figure 4: BHT content in tablets after 5 days storage at 50°C.

- Residual BHT ~ particle size.
- Using larger particle size

  → lower specific surface area

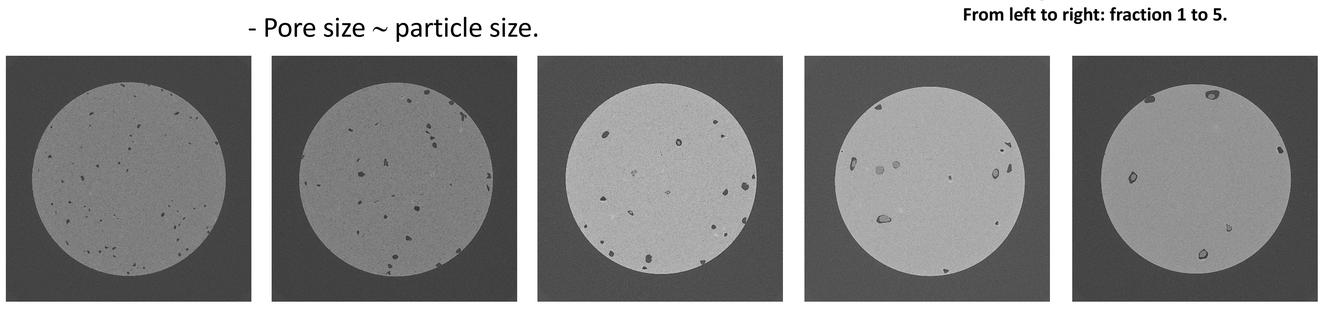
  → sublimation ↓
- **Fraction 4**: 43.3 ± 1.2% BHT remaining.
- **Fraction 5**: unreliable data due to content uniformity issues.

Pore formation:

Appearance: - Pores observed at tablet surface for all fractions.

- Pore size ~ particle size.

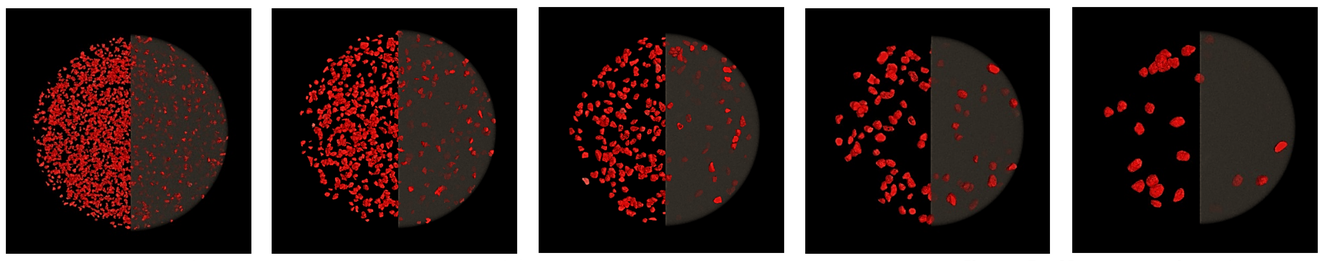
Figure 5: Top view of a heat-treated tablet containing different BHT size fractions. From left to right: fraction 1 to 5.



XµCT scans: - Pore formation both at surface and in core of tablet.

- Using larger particle size → BHT residue visible on XµCT.

Figure 6: XµCT scan of the middle section of a heat-treated tablet containing different BHT size fractions. From left to right: fraction 1 to 5.



3D-reconstruction: - Red spots = pores without BHT residue.

- Slower sublimation rate of BHT in the core of the tablet.

Figure 7: 3D-reconstruction of a heat-treated tablet containing different BHT size fractions. From left to right: fraction 1 to 5.