

## ORODISPERSIBLE TABLETS: “USING NATURAL SUPERDISINTEGRANTS”

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### ABSTRACT

Orodispersible tablets (ODTs) represent a significant advancement in pharmaceutical technology, offering rapid disintegration and dissolution in the oral cavity without requiring water intake. This comprehensive review examines the application of natural superdisintegrants in ODT formulations, emphasizing their mechanism of action, advantages over synthetic alternatives, and practical applications in modern pharmaceutical science. Natural superdisintegrants such as fenugreek seed mucilage, *Plantago ovata* (psyllium) husk, guar gum, and other plant-derived polymers have demonstrated comparable or superior disintegration properties to synthetic agents while offering biocompatibility, biodegradability, and cost-effectiveness.<sup>[1,2]</sup> This paper provides an in-depth analysis of formulation techniques, optimization strategies using Quality by Design (QbD) approaches, evaluation parameters, and therapeutic applications of ODTs incorporating natural superdisintegrants. Special emphasis is placed on BCS Class II drugs where enhanced bioavailability through rapid disintegration can significantly improve therapeutic outcomes. Current regulatory perspectives, challenges in scale-up manufacturing, and future directions for natural superdisintegrant research are also discussed. The review synthesizes recent literature and clinical evidence to provide a comprehensive understanding of ODT technology for pharmaceutical researchers, formulators, and academic professionals.

**KEYWORDS:** Orodispersible tablets, natural superdisintegrants, bioavailability, drug delivery, plant polymers, formulation optimization.

## 1. INTRODUCTION

### 1.1 Background and Historical Development

The pharmaceutical industry has continuously evolved to provide more effective and patient-compliant dosage forms. Traditional solid oral dosage forms, particularly tablets, have long been the most popular and economical choice for drug delivery.<sup>[3]</sup> However, several patient populations face challenges with conventional tablets, including pediatric patients, geriatric individuals with dysphagia, those with reduced salivary flow, and patients requiring rapid therapeutic intervention.<sup>[4]</sup> These limitations led to the development of orodispersible tablets (ODTs), also known as mouth-dissolving tablets, fast-dissolving tablets (FDTs), melt tablets, or oro-dispersible tablets.

The concept of rapidly disintegrating tablets emerged in the 1980s, with significant development occurring through the 1990s and 2000s.<sup>[5]</sup> Early formulations relied primarily on synthetic superdisintegrants such as croscarmellose sodium (CCS), sodium starch glycolate (SSG), and crospovidone. However, growing environmental concerns, patient preference for natural products, and recognition of the advantages of plant-derived excipients have shifted focus toward natural superdisintegrants.<sup>[2,6]</sup>

### 1.2 Definition and Classification of ODTs

Orodispersible tablets are defined as tablets that disintegrate and/or dissolve rapidly in the mouth, typically within 3 minutes as per regulatory guidelines, without requiring water for intake.<sup>[7]</sup> This unique characteristic offers several advantages:

- Rapid onset of action for therapeutic effect
- Reduced choking hazard, particularly for elderly and pediatric patients
- Improved patient compliance and convenience
- Potential for improved bioavailability through pregastric absorption
- No requirement for water intake (beneficial in travel or water-scarce situations)<sup>[4]</sup>
- ODTs can be classified based on various criteria:
- **Based on disintegration mechanism:** Superdisintegrant-based, compressed porous tablets, lyophilized tablets, effervescent tablets, wafer tablets
- **Based on drug type:** Suitable for BCS Class I, II, III, and IV drugs; particularly beneficial for Class II drugs with poor solubility
- **Based on formulation approach:** Direct compression, wet granulation, freeze-drying, sublimation

### 1.3 Significance of Natural Superdisintegrants

Natural superdisintegrants have garnered considerable attention in recent pharmaceutical research for multiple compelling reasons.<sup>[8]</sup> The global shift toward natural and sustainable products in pharmaceuticals has created a paradigm where natural polymers are viewed as equal or superior alternatives to synthetic agents. Key reasons for this shift include:

1. **Economic advantage:** Natural superdisintegrants are derived from agricultural byproducts and are significantly less expensive than synthetic alternatives<sup>[6]</sup>
2. **Safety and biocompatibility:** Plant-derived polymers have demonstrated long histories of safe use, with minimal adverse effects<sup>[2]</sup>

3. **Environmental sustainability:** Natural polymers are biodegradable and environmentally friendly, aligning with global sustainability goals<sup>[6]</sup>
4. **Regulatory acceptance:** Major regulatory agencies recognize many natural polymers as GRAS (Generally Recognized as Safe) substances<sup>[1]</sup>
5. **Therapeutic potential:** Some natural polymers offer additional therapeutic benefits beyond their superdisintegrant properties<sup>[9]</sup>

## 2. Natural Superdisintegrants: Overview and Classification

### 2.1 Categories of Natural Superdisintegrants

Natural superdisintegrants can be classified into distinct categories based on their botanical origin and chemical composition:

#### 2.1.1 Mucilages and Gums from Seeds

**Table 1: Comparative characteristics of seed-derived natural superdisintegrants.**

Source	Scientific Name	Active Component	Key Property
Fenugreek seeds	Trigonella foenum-graecum	Galactomannan	High swelling index
Psyllium/Isabgol	Plantago ovata Forsk	Polysaccharide mucilage	Rapid water absorption
Guar seeds	Cyamopsis tetragonoloba	Galactomannan	Enhanced viscosity
Lepidium sativum	Garden cress	Mucilage	Binding and disintegrant
Chia seeds	Salvia hispanica	Hydrocolloid mucilage	High water-binding capacity

#### 2.1.2 Mucilages and Gums from Plant Materials

- **Isabgol husk:** Extracted from *Plantago ovata*, provides excellent swelling properties (swelling index:  $89 \pm 2.2\%$ )<sup>[10]</sup>
- **Okra gum:** Rich in polysaccharides, demonstrates dual properties as superdisintegrant and binder
- **Dehydrated banana powder:** FDA-approved natural material with disintegrant properties<sup>[10]</sup>
- **Mango seed mucilage:** Promising biodegradable polymer for ODT applications

#### 2.1.3 Seaweed-Derived Polymers

- **Sodium alginate:** From brown seaweeds, exhibits swelling and wicking properties
- **Carrageenan:** Complex sulfated polysaccharide with rheological properties

## 2.2 Physicochemical Properties of Key Natural Superdisintegrants

### 2.2.1 Fenugreek Seed Mucilage

**Source and Composition:** Fenugreek seeds (*Trigonella foenum-graecum*) contain approximately 40-50% mucilage composed of galactomannan polymers. The extracted mucilage consists of galactose, mannose, and other monosaccharide units linked through glycosidic bonds.<sup>[11]</sup>

#### Key Properties

- Swelling index: 500-600% w/v
- Particle size: 50-200  $\mu\text{m}$  (when milled)
- Solubility: Forms colloidal suspension in water
- pH stability: Stable across pH 1-8
- Hygroscopicity: Moderate moisture absorption capacity

**Advantages**

- Superior disintegration compared to synthetic agents like Ac-di-sol<sup>[11]</sup>
- Cost-effective and easy to extract
- Non-toxic with long history of use in traditional medicine
- Additional nutritional properties (protein and fiber content)

**Challenges**

- Batch variability from agricultural sources
- Potential allergenicity in sensitive individuals
- Viscosity control during formulation

**2.2.2 Plantago ovata (Psyllium) Husk**

**Source and Composition:** Psyllium husk, the seed coat of *Plantago ovata*, contains approximately 30% polysaccharide mucilage composed primarily of arabinoxylans and other neutral polysaccharides.<sup>[12]</sup>

**Key Properties**

- Swelling index: 85-95% v/v
- Disintegration time: 119-185 seconds at 8-16 mg concentration<sup>[12]</sup>
- Water absorption ratio: Up to 86% with optimal formulations<sup>[12]</sup>
- Wetting time: 8-11 seconds for optimized formulations<sup>[12]</sup>
- Bulk density: 0.4-0.5 g/cm<sup>3</sup>

**Advantages**

- Significantly faster dissolution rate than synthetic disintegrants
- High water absorption ratio enabling rapid tablet disintegration
- Already FDA-approved for use in pharmaceutical formulations
- Superior bioavailability enhancement for poorly soluble drugs like meloxicam<sup>[12]</sup>

**Challenges**

- Source limitation and seasonal variation
- Regulatory requirement for botanical sourcing documentation
- Potential interaction with certain drug molecules

**2.2.3 Guar Gum**

**Source and Composition:** Derived from the endosperm of guar bean (*Cyamopsis tetragonoloba*), containing approximately 80% galactomannan with a galactose-to-mannose ratio of 1:2.<sup>[13]</sup>

**Key Properties**

- Viscosity: 500-8000 cP (varies with concentration and grade)
- Swelling capacity: Moderate (200-250%)
- Solubility: Partially soluble, forms viscous colloidal dispersion
- Hydration time: 1-2 hours for complete hydration

- Molecular weight: 200,000-300,000 Daltons

### Advantages

- Dual functionality as superdisintegrant and binder
- Cost-effective with global agricultural availability
- Improved drug dissolution at lower concentrations (4-6% w/w)
- Non-toxic and biodegradable

### Challenges

- Viscosity effects requiring optimization with other excipients
- Limited swelling properties compared to other natural polymers
- Microbial contamination risk requiring antimicrobial treatment

## 3. Mechanisms of Disintegration: Theory

### 3.1 Molecular Mechanisms of Superdisintegrant Action

Superdisintegrants act through multiple synergistic mechanisms to achieve rapid tablet disintegration and drug dissolution.<sup>[14]</sup> Understanding these mechanisms is crucial for optimal formulation design.

#### 3.1.1 Swelling Mechanism

The swelling mechanism represents the primary disintegration pathway for most natural superdisintegrants. When tablet comes into contact with aqueous medium or saliva:

1. **Water penetration:** Water molecules interact with polar groups on the polymer backbone through hydrogen bonding.
2. **Polymer relaxation:** Cross-linked or semi-cross-linked polymer chains relax, increasing molecular volume.
3. **Osmotic pressure development:** Differential osmotic pressure between interior and exterior of swelling polymer exceeds tablet binding forces.
4. **Tablet disruption:** Accumulated swelling pressure causes matrix fracture and tablet disintegration.<sup>[14]</sup>

**Mathematical representation:** Swelling capacity can be quantified using the swelling index (SI):

$$SI = \left( \frac{\text{Volume of tablet after swelling} - \text{Original volume of tablet}}{\text{Original volume of tablet}} \right) \times 100\%$$

Natural superdisintegrants like fenugreek demonstrate swelling indices of 500-600%, significantly exceeding many synthetic alternatives.<sup>[11]</sup>

#### 3.1.2 Wicking (Capillary Action)

Wicking represents the second major disintegration mechanism, particularly relevant for superdisintegrants with fibrous particle morphology<sup>[14]</sup>:

1. **Capillary network formation:** Fiber-like particles create capillary channels within tablet matrix.
2. **Water transport:** Capillary forces pull aqueous medium into tablet via these channels.
3. **Rapid water distribution:** Water reaches tablet center quickly through capillary networks.
4. **Matrix dissolution:** Wetting enables rapid drug dissolution and tablet disintegration.

This mechanism is particularly important for croscarmellose sodium, which exhibits primary disintegration through wicking rather than swelling.<sup>[15]</sup>

### 3.1.3 Heat of Wetting

Several natural polymers exhibit exothermic properties when exposed to aqueous medium:

1. **Energetic dissolution:** Polymer hydration releases thermal energy.
2. **Temperature elevation:** Local temperature increase disrupts tablet binding.
3. **Accelerated disintegration:** Heat facilitates water penetration and polymer swelling.

The magnitude of heat of wetting for natural polymers is typically lower than synthetic agents but contributes to overall disintegration efficiency.<sup>[14]</sup>

### 3.1.4 Deformation Recovery and Particle Repulsion

Some polymers exhibit elasticity that enables spring-like recovery:

1. **Compressed state:** Superdisintegrant particles exist under compression in tablet.
2. **Water exposure:** Water interaction causes elastic deformation recovery.
3. **Repulsion forces:** Recovered particles push against adjacent matrix.
4. **Mechanical disruption:** Cumulative repulsion forces exceed tablet tensile strength.

## 4. Formulation Strategies for ODTs with Natural Superdisintegrants

### 4.1 Pre-formulation Studies

#### 4.1.1 Drug Selection Criteria

Optimal drug candidates for ODT formulation using natural superdisintegrants meet specific criteria:

**BCS Classification:** BCS Class II drugs (low solubility, high permeability) represent ideal candidates because:

- Enhanced bioavailability through pregastric absorption
- Rapid disintegration improves oral dissolution rate
- Natural superdisintegrants' swelling properties aid wetting and dissolution
- Examples: meloxicam, carvedilol, ondansetron, itraconazole<sup>[3]</sup>

#### Physicochemical Properties Ideal for ODT Formulation

- Dose: < 1000 mg (preferably < 500 mg)
- Molecular weight: 200-500 Da
- pKa: 2-7 for weak acid/base drugs
- LogP: 1.5-6 (good balance of hydrophilicity and lipophilicity)
- Half-life: 1-4 hours
- Melting point: > 100°C
- Stability: Non-hygroscopic, non-photosensitive

#### 4.1.2 Excipient Compatibility Studies

Critical compatibility evaluations ensure absence of interactions:

**Analytical Techniques:**

1. **Fourier Transform Infrared (FTIR) Spectroscopy:** Identifies chemical interactions through peak shifts.
2. **Differential Scanning Calorimetry (DSC):** Detects polymorphic changes and thermal behavior alterations.
3. **X-ray Diffraction (XRD):** Confirms crystallinity maintenance.
4. **High-Performance Liquid Chromatography (HPLC):** Quantifies drug degradation under stress conditions.

**Stress Testing Conditions**

- Temperature:  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$
- Relative humidity:  $75\% \pm 5\% \text{ RH}$
- Time duration: 14-30 days
- Drug-excipient ratios: 1:0.5, 1:1, 1:2, 1:4 (w/w)

**4.2 Formulation Development Approaches****4.2.1 Direct Compression Method**

Direct compression remains the most practical and economical approach for ODT manufacturing<sup>[16]</sup>:

**Advantages**

- Single-step process reducing manufacturing time.
- Minimal equipment investment.
- Lower product degradation (no wet granulation or heat exposure).
- Suitable for moisture-sensitive drugs.
- Excellent for thermolabile natural superdisintegrants.

**Process Steps**

1. **Screening:** Pass all excipients through appropriate sieves (100-200 mesh)
2. **Blending Phase I:** Combine API with glidants (0.5-1% colloidal silicon dioxide) for 5 minutes
3. **Addition of Superdisintegrants:** Add natural superdisintegrant (3-8% w/w) and blend for 10 minutes
4. **Addition of Lubricants:** Add magnesium stearate (0.5-2% w/w) and blend for 2-3 minutes (critical: excessive blending causes moisture absorption)
5. **Filling and Compression:** Fill die cavity and compress at predetermined force
6. **Ejection:** Carefully eject tablets to prevent capping or lamination

**Superdisintegrant Concentration Optimization**

Natural superdisintegrants typically require concentrations of 3-8% w/w for optimal disintegration:

- **Fenugreek mucilage:** 4-6% w/w demonstrated optimal performance<sup>[11]</sup>
- **Psyllium husk:** 6-8% w/w (16 mg per tablet) showed superior dissolution<sup>[12]</sup>
- **Guar gum:** 4-5% w/w for dual superdisintegrant-binder properties<sup>[13]</sup>

Concentrations exceeding 8% may compromise tablet hardness and stability.

#### 4.2.2 Wet Granulation Method

Though more complex than direct compression, wet granulation offers advantages for certain formulations:

##### Process Overview

1. **Mixing:** Blend API with part of diluent for 5-10 minutes.
2. **Granulation:** Add binder solution (1-5% starch paste or 5-10% PVP solution) gradually while mixing.
3. **Drying:** Dry granules at 60-80°C for 30-45 minutes to reduce moisture to < 3%
4. **Sizing:** Pass through appropriate sieve (12-16 mesh)
5. **Addition of superdisintegrant:** Add natural superdisintegrant (add at lubrication step: post-granulation addition prevents moisture absorption)
6. **Lubrication:** Add magnesium stearate and colloidal silica.
7. **Compression:** Compress at appropriate force.

##### Advantages for Natural Superdisintegrants

- Post-granulation addition of superdisintegrant prevents premature interaction with moisture.
- Improved flow properties of granules aid formulation.
- Better suited for hygroscopic natural polymers.

#### 5. Evaluation and Characterization of ODTs

##### 5.1 Pre-compression Parameters (Powder Characterization)

###### 5.1.1 Micromeritic Properties

###### Angle of Repose ( $\theta$ )

- **Method:** Fixed-funnel or rotating-cylinder method
- **Principle:** Gravitational angle at which powder particles remain stable on inclined plane
- **Evaluation:**  $\theta < 30^\circ$  indicates excellent flow;  $30-40^\circ$  acceptable flow
- **Formula:**  $\tan \theta = \frac{h}{r}$  (h = height, r = radius of cone)
- **Significance:** Predicts hopper flow and die filling uniformity

###### Bulk Density ( $\rho_b$ ) and Tapped Density ( $\rho_t$ )

- **Bulk density:** Weight of powder per unit volume in non-compacted state
- **Tapped density:** Density after subjecting to standardized mechanical tapping
- **Formula:** Hausner ratio =  $\frac{\rho_t}{\rho_b}$  (optimal: 1.25-1.35)
- **Interpretation:** HR < 1.25 indicates excellent flow; HR > 1.6 indicates poor flow

###### Compressibility Index

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100\%$$

- CI < 15%: Good flow properties
- CI 15-25%: Acceptable flow
- CI > 25%: Poor flow

### 5.1.2 Moisture Content and Hygroscopicity

#### Karl Fischer Titration (KFT)

- **Principle:** Electrochemical determination of water content
- **Target moisture:** < 3% for optimal tablet performance
- **Natural superdisintegrants:** Typically absorb 2-5% moisture; requires environmental control

#### Hygroscopicity Evaluation

- **Method:** Expose powder (1 g) to controlled humidity (75% RH, 25°C) for 24 hours
- **Calculation:** % moisture increase = [(final weight - initial weight) / initial weight] × 100%
- **Significance:** High hygroscopicity indicates need for moisture protection during storage

## 5.2 Post-compression Parameters (Tablet Quality Control)

### 5.2.1 Tablet Hardness and Tensile Strength

#### Hardness Testing

- **Instrument:** Hardness tester (Monsanto, Monsanto, or differential scanning tester)
- **Unit:** Kilogram-force (kgf) or Newton (N)
- **Target range:** 50-150 N for ODTs (lower than conventional tablets for rapid disintegration)
- **Testing procedure:** Minimum 10 tablets from each batch

#### Interpretation

- Hardness < 50 N: Tablet friability and breakage risk
- Hardness 50-100 N: Optimal for rapid disintegration ODTs
- Hardness 100-150 N: Acceptable with minimal disintegration compromise
- Hardness > 150 N: Risk of delayed disintegration exceeding regulatory limits

#### Tensile Strength Calculation

$$\text{Tensile strength} = \frac{2F}{\pi DT}$$

Where F = crushing force (N), D = tablet diameter (mm), T = tablet thickness (mm)

### 5.2.2 Friability Testing (USP <1216>)

**Objective:** Determine tablet resistance to abrasion and breakage during handling, packing, and transport.

#### Procedure

1. Weigh 20 tablets to nearest 0.1 mg (initial weight, W<sub>i</sub>)
2. Place in Roche friability apparatus rotating at 25 rpm for 100 revolutions (4 minutes)
3. Remove tablets and dust with soft brush
4. Weigh tablets again (W<sub>f</sub>)

#### Calculation

$$\text{Friability (\%)} = \left( \frac{W_i - W_f}{W_i} \right) \times 100\%$$

**Acceptance Criteria:** Maximum 1% weight loss acceptable for tablets

**Special Consideration for ODTs:** ODTs naturally friable due to rapid disintegration excipients; friability should not exceed 1.5% with natural superdisintegrants.

### 5.2.3 Content Uniformity (USP < 905 >)

#### Assay by HPLC

1. Dissolve tablet in mobile phase
2. Filter through 0.45  $\mu\text{m}$  filter
3. Analyze by HPLC at predetermined wavelength
4. Calculate drug content as % of label claim

**Acceptance:** 85-115% of label claim for individual tablets

#### Relative Standard Deviation (RSD)

- Individual tablet RSD should be < 10%
- Batch RSD should be < 5%

### 5.3 Disintegration Testing

#### 5.3.1 USP Disintegration Test (USP < 701 >)

##### Apparatus and Conditions

- **Medium:** pH 6.8 phosphate buffer (pH varied based on formulation: 1.2 for gastric simulation, 6.8 for intestinal)
- **Temperature:** 37°C  $\pm$  2°C
- **Volume:** 800 mL per test

##### Standard ODT Test Conditions

- **Disk:** No disk used (ODT standard)
- **Apparatus:** Standard disintegration basket-rack assembly
- **Acceptance:** Complete disintegration within 3 minutes

##### Procedure

1. Place one tablet in each of six tubes
2. Add disintegration medium maintained at 37°C
3. Basket oscillates 28-32 times per minute (up-and-down motion)
4. Record time for complete disintegration
5. Tablet completely disintegrated when no particles remain on mesh (10-mesh screen)

##### Limitations of USP Method for ODTs

- Mechanical agitation in USP apparatus exceeds conditions in oral cavity.<sup>[19]</sup>
- Results often underestimate actual in vivo disintegration time.
- Does not accurately simulate saliva-mediated disintegration.

## 5.4 Dissolution Testing (USP < 711>)

### 5.4.1 Apparatus and Experimental Design

#### Apparatus Selection

- **Apparatus 1 (Basket method):** Rotating basket at 100 rpm; preferred for rapidly disintegrating tablets.
- **Apparatus 2 (Paddle method):** Rotating paddle at 50-100 rpm; suitable for non-disintegrating formulations.

#### Standard Conditions

- **Medium volume:** 900 mL
- **Temperature:** 37°C ± 0.5°C
- **pH:** pH 6.8 phosphate buffer (can vary: pH 1.2, 4.5 depending on monograph)
- **Rotation speed:** 50 rpm (Apparatus 2) or 100 rpm (Apparatus 1)
- **Sampling times:** 5, 10, 15, 20, 30, 45, 60 minutes (adjust based on drug)

## 6.1. Challenges and Limitations of Natural Superdisintegrants

### 1.1 Batch-to-Batch Variability

#### Root Causes

1. **Agricultural factors:** Climate variations, soil composition, harvesting methods affect polymer content.
2. **Storage conditions:** Moisture absorption, temperature exposure during storage alters properties.
3. **Processing variability:** Drying temperature, extraction efficiency, milling procedures impact final quality.

#### Impact on Formulation

- ±15-30% variation in swelling properties between batches
- Disintegration time variability of 20-50 seconds between batches
- Requires batch testing before formulation initiation
- Necessitates specification widening affecting formulation robustness

### 1.2 Allergenicity and Safety Concerns

#### Documented Allergic Reactions

- **Fenugreek:** Cross-reactivity with peanuts and chickpeas in sensitive individuals.
- **Plantago ovata:** Rare respiratory sensitization in manufacturing workers.
- **Guar gum:** Allergic reactions documented in individuals with legume sensitivity.<sup>[6]</sup>

### 1.3 Hygroscopicity and Storage Stability

#### Challenges

- Natural superdisintegrants absorb 2-5% moisture under high humidity conditions
- Moisture absorption causes:
  - Reduced swelling efficiency
  - Increased tablet friability
  - Potential microbial contamination
  - Reduced drug stability (especially for moisture-sensitive APIs)

### Mitigation Approaches

- **Storage conditions:**  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ,  $60\% \pm 5\%$  relative humidity
- **Packaging:** Moisture-barrier packaging (aluminum foil blisters with desiccant)
- **Pre-drying:** Heat treatment of natural superdisintegrant before formulation ( $60\text{-}80^{\circ}\text{C}$  for 2-4 hours)
- **Shelf-life recommendations:** 18-24 months (shorter than synthetic alternatives)

### 1.4 Microbial Contamination Risk

#### Potential Issues

- Plant-derived materials may harbor bacteria, fungi, or endotoxins
- Natural superdisintegrants lack inherent antimicrobial properties (unlike some synthetic polymers)
- High water-binding capacity creates environment supporting microbial growth

#### Contamination Prevention

1. **Raw material testing:** Microbial limits testing per USP < 2023> (bacterial count  $< 10^2$  CFU/g, absence of pathogens)
2. **Sterilization procedures**
  - Gamma irradiation (2-2.5 kGy) for heat-sensitive materials
  - Ethylene oxide sterilization (may affect polymer properties)
  - Autoclaving (40 min,  $121^{\circ}\text{C}$ ) with moisture monitoring
  -

### 6.2. Quality by Design (QbD) in Regulatory Submission

#### ICH Q8, Q9, Q10, Q11 Guidelines Compliance

- **Q8:** Pharmaceutical development documentation
- **Q9:** Quality risk assessment for identified critical process parameters
- **Q10:** Lifecycle approach to quality management
- **Q11:** Process characterization and definition of design space

#### Required Regulatory Documentation

##### 1. Chemistry section

- Drug substance characterization
- Drug product composition and specifications
- Analytical methods validation
- Stability data (3-month accelerated:  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $75\% \pm 5\%$  RH; 6-month intermediate:  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $65\% \pm 5\%$  RH)

### 6.3. Nanotechnology Applications

#### Nanoparticle-Based Delivery with Natural Superdisintegrants

Emerging research combines nanoparticle technology with natural superdisintegrants:

1. **Nano-carrier systems:** Drug nanoparticles dispersed in ODT with natural superdisintegrants
  - Enhanced surface area for dissolution
  - Synergistic disintegration + nanoparticle properties

- Improved bioavailability for poorly soluble drugs
- 2. Nano-superdisintegrants:** Nanoparticles of natural polymers (100-500 nm)
- Increased surface area for water interaction
  - Enhanced swelling efficiency at lower concentrations
  - Potential allergenicity reduction through structural modification

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