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Nitric Oxide–Generating Mouth Dissolving Tablets in Peptic Ulcer Disease: Formulation Approaches, Therapeutic Mechanisms, and Future Perspectives

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Abstract

Peptic ulcer disease is a common gastrointestinal disorder characterized by damage to the protective lining of the stomach or upper intestine and is associated with factors such as gastric acid, *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs, and other contributing conditions. Nitric oxide (NO) has an important role in gastrointestinal protection by supporting mucosal blood flow and tissue repair. Conventional oral dosage forms may have limitations including difficulty in swallowing, dependence on water, delayed relief, and reduced patient convenience. The present work focuses on NitroCure, a nitric oxide-generating mouth dissolving tablet (MDT) developed as a patient-friendly approach for peptic ulcer management. The formulation was designed to provide rapid tablet dispersion while maintaining satisfactory mechanical strength, palatability, and pharmaceutical quality. Croscarmellose sodium was incorporated to promote rapid disintegration, mannitol to improve taste and mouthfeel, PVP K-30 as a binder, and magnesium stearate and talc as processing aids, while citric acid supported rapid dispersion and palatability. The prepared tablets were evaluated for relevant pharmaceutical parameters, including flow properties, weight variation, hardness, friability, wetting time, and disintegration. The formulation demonstrated satisfactory flow properties, uniformity, adequate mechanical strength, and rapid dispersion. The reported friability was 0.76%, indicating good resistance to mechanical stress, while the wetting time was 36.5 seconds, demonstrating rapid water absorption and supporting quick tablet dispersion. Overall, NitroCure MDT showed desirable pharmaceutical characteristics and met the intended quality requirements. The developed formulation represents a promising patient-friendly platform for further

investigation of nitric oxide-based approaches in peptic ulcer management. Further optimization, stability studies, and appropriate in-vitro and in-vivo investigations are required to establish its therapeutic potential.

Keywords

Peptic ulcer disease, Mouth dissolving tablets, Nitric oxide, Oral drug delivery system, Superdisintegrants, Gastric mucosal healing.

1.Introduction

1.1 Background

Peptic ulcer disease (PUD) is a chronic gastrointestinal disorder characterized by the development of ulcers in the lining of the stomach (gastric ulcer) or the proximal part of the small intestine (duodenal ulcer). It remains a major global health concern because of its high prevalence, recurrent nature, and associated complications such as gastrointestinal bleeding, perforation, and gastric outlet obstruction. The disease develops when the balance between aggressive factors, including gastric acid, pepsin, *Helicobacter pylori* infection, and prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), is disrupted and exceeds the protective mechanisms of the gastric mucosa. Lifestyle factors such as smoking, excessive alcohol intake, psychological stress, and unhealthy dietary habits further contribute to disease progression.

Current pharmacological treatment mainly consists of proton pump inhibitors (PPIs), H_2-receptor antagonists, antacids, mucosal protective agents, and antibiotic therapy for *H. pylori* eradication. Although these therapies effectively reduce gastric acid secretion and promote ulcer healing, they may require repeated administration, exhibit delayed onset of action, and are sometimes associated with adverse effects, recurrence, poor patient adherence, and the development of antimicrobial resistance. Therefore, there is a continuous need to explore innovative drug delivery systems capable of improving therapeutic outcomes and patient compliance.

Mouth dissolving tablets (MDTs), also known as orally disintegrating tablets, represent an advanced oral drug delivery system designed to disintegrate rapidly in the oral cavity without the need for water. Their ease of administration makes them particularly suitable for pediatric, geriatric, dysphagic, and bedridden patients. Rapid tablet disintegration can facilitate faster drug availability, improve patient acceptance, and enhance treatment adherence compared with conventional solid dosage forms.

Nitric oxide (NO) is an important endogenous signaling molecule involved in numerous physiological functions, including regulation of vascular tone, modulation of inflammation, maintenance of gastric mucosal integrity, stimulation of mucus and bicarbonate secretion, and enhancement of tissue repair. Experimental studies have demonstrated that nitric oxide improves gastric microcirculation, reduces oxidative stress, inhibits leukocyte adhesion, and accelerates healing of damaged gastric mucosa. These protective actions suggest that nitric oxide-generating formulations may provide therapeutic advantages beyond acid suppression alone.

The integration of nitric oxide-generating systems with mouth dissolving tablet technology has emerged as a promising strategy for peptic ulcer management. By combining rapid tablet disintegration with localized nitric oxide generation, this approach has the potential to provide faster therapeutic action, improve mucosal healing, enhance patient convenience, and overcome several limitations associated with conventional oral formulations.

1.2 Need of the Review

Despite significant advances in anti-ulcer therapy, existing treatment approaches primarily focus on reducing gastric acid secretion rather than actively promoting regeneration of the damaged gastric mucosa. In addition, conventional tablets may present challenges such as delayed onset of action, difficulty in swallowing, reduced patient compliance, and repeated dosing requirements. Recent research has highlighted the gastro protective role of nitric oxide and the advantages of mouth dissolving tablet technology; however, comprehensive reviews integrating these two concepts remain limited. Therefore, there is a need to systematically review the available evidence regarding nitric oxide-generating mouth dissolving tablets, their formulation strategies, mechanisms of action, evaluation methods, therapeutic benefits, and future clinical prospects.

1.3 Objectives of the Review

The objectives of this review are to:

- Review the pathophysiology and current management strategies of peptic ulcer disease.
- Discuss the physiological role of nitric oxide in gastric mucosal protection and ulcer healing.
- Describe the principles and formulation approaches of mouth dissolving tablets.
- Summarize the excipients and evaluation parameters commonly employed in nitric oxide-generating MDT formulations.
- Evaluate the potential therapeutic advantages of nitric oxide-generating mouth dissolving tablets over conventional dosage forms.
- Identify current research gaps and future directions for the development of advanced MDT-based therapies for peptic ulcer disease.

1.4 Significance of the Review

This review provides a comprehensive overview of nitric oxide-generating mouth dissolving tablets as an emerging strategy for peptic ulcer therapy. It highlights the relationship between nitric oxide-mediated mucosal protection and modern oral drug delivery technology while summarizing current scientific evidence on formulation design, evaluation, and therapeutic applications. The review serves as a valuable resource for pharmacy students, researchers, formulation scientists, and healthcare professionals by presenting updated knowledge in a clear and systematic manner. Furthermore, it identifies opportunities for future research aimed at improving treatment efficacy, patient compliance, formulation stability, and clinical outcomes in peptic ulcer disease through innovative drug delivery approaches.

2. Literature Search Methodology

A comprehensive literature search was conducted to collect relevant and reliable scientific information regarding peptic ulcer disease, nitric oxide, mouth dissolving tablets (MDTs), and their applications in gastroprotective drug delivery. The review was based on published peer-reviewed research articles, review papers, standard pharmaceutical textbooks, and pharmacopeial publications to ensure scientific accuracy and comprehensive coverage of the topic.

2.1 Databases Searched

The literature was retrieved from internationally recognized electronic databases, including:

- PubMed/MEDLINE
- Google Scholar
- Scopus
- ScienceDirect
- SpringerLink
- Wiley Online Library
- Taylor & Francis Online
- Nature Reviews
- MDPI Journals
- Elsevier Journals
- The Lancet
- New England Journal of Medicine (NEJM)
- British Journal of Pharmacology
- World Journal of Gastroenterology

3. Overview of the Topic

Definition

Nitric oxide (NO)-generating mouth dissolving tablets (MDTs) are a novel oral drug delivery system designed to disintegrate rapidly in the oral cavity without the need for water while releasing or generating nitric oxide to exert therapeutic effects. These formulations combine the advantages of orally disintegrating tablet technology with the gastroprotective properties of nitric oxide. Nitric oxide acts as an endogenous signaling molecule that promotes gastric mucosal defense by increasing blood flow, stimulating mucus and bicarbonate secretion, reducing oxidative stress, and enhancing tissue repair. Consequently, NO-generating MDTs have emerged as a promising strategy for improving the treatment of peptic ulcer disease by providing rapid drug release, enhanced patient compliance, and improved therapeutic outcomes.

History

Peptic ulcer disease has affected humans for centuries; however, major advances in its understanding have occurred over the past few decades. Before the 1980s, excessive gastric acid secretion, stress, and dietary factors were considered the principal causes of ulcer formation. A landmark discovery by Barry J. Marshall and J. Robin Warren in 1982 demonstrated that *Helicobacter pylori* infection is a major etiological factor in gastric ulcer disease, revolutionizing ulcer treatment through antibiotic-based eradication therapy.

During the late 1980s and early 1990s, nitric oxide was identified as a critical biological mediator involved in vascular regulation and gastric mucosal protection. Research subsequently confirmed that nitric oxide maintains mucosal integrity by improving microcirculation, reducing inflammation, inhibiting leukocyte adhesion, and accelerating ulcer healing. At the same time, mouth dissolving tablet technology evolved as an innovative oral dosage form capable of rapid disintegration without water. The integration of nitric oxide-generating systems with MDT technology represents a recent advancement aimed at combining gastroprotective activity with improved drug delivery and patient convenience.

Classification

Nitric oxide-generating mouth dissolving tablets can be classified according to different pharmaceutical and formulation criteria.

1. Based on Nitric Oxide Source

- Organic nitrate-based formulations
- Nitrite-based formulations
- Nitric oxide donor-based formulations
- Acid-activated nitric oxide-generating systems

2. Based on Manufacturing Method

- Direct compression
- Freeze-drying (lyophilization)
- Molding technique
- Spray drying
- Sublimation
- Mass extrusion

3. Based on Disintegration Mechanism

- Swelling-based systems
- Wicking-based systems
- Effervescent systems
- Combined swelling and wicking systems

4. Based on Drug Delivery Characteristics

- Conventional mouth dissolving tablets
- Orally disintegrating tablets (ODTs)
- Fast dissolving tablets (FDTs)
- Rapidly disintegrating tablets

Advantages

Nitric oxide-generating mouth dissolving tablets provide several pharmaceutical and therapeutic advantages over conventional oral dosage forms.

- Rapid disintegration and drug release in the oral cavity.
- Administration without water, improving convenience.
- Faster onset of therapeutic action.
- Improved patient compliance, especially in pediatric, geriatric, and dysphagic patients.
- Enhanced gastric mucosal blood flow through nitric oxide release.
- Promotion of mucus secretion and tissue regeneration.
- Reduction in gastric inflammation and oxidative stress.
- Better patient acceptance due to pleasant mouthfeel.
- Potential improvement in ulcer healing beyond acid suppression alone.
- Portable and convenient dosage form suitable for emergency or outpatient use.
- Reduced swallowing difficulties and improved treatment adherence.

Disadvantages

Despite their advantages, these formulations also have certain limitations.

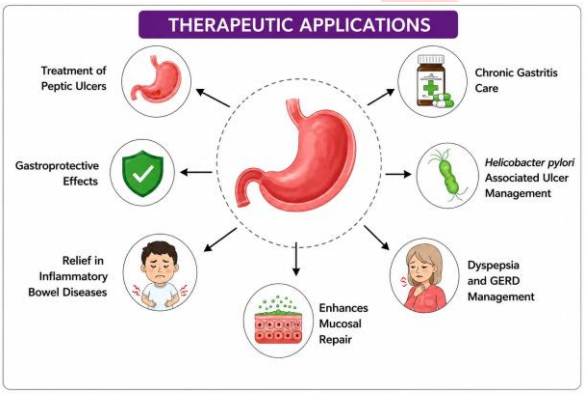
- High sensitivity to moisture requiring specialized packaging.
- Lower mechanical strength than conventional tablets.
- Stability challenges associated with nitric oxide-generating components.
- More complex formulation and manufacturing process.
- Higher production cost than conventional tablets.
- Limited availability of long-term clinical evidence.
- Requirement for careful optimization of excipient compatibility.
- Possible degradation of nitric oxide precursors during storage.
- Difficulties in large-scale commercial manufacturing.
- Need for stringent quality control during production.

Applications

Nitric oxide-generating mouth dissolving tablets have potential applications in several therapeutic and pharmaceutical areas.

Gastrointestinal Applications

- Management of peptic ulcer disease.
- Enhancement of gastric mucosal healing.
- Protection against gastric mucosal injury.
- Adjunctive therapy with conventional anti-ulcer medications.



Pharmaceutical Applications

- Advanced oral drug delivery systems.
- Development of fast-acting oral formulations.
- Patient-friendly dosage forms.
- Research on nitric oxide-mediated drug delivery technologies.

4. Detailed Discussion

4.1 Mechanism of Peptic Ulcer Disease and Role of Nitric Oxide

- Pathophysiology of peptic ulcer disease
- Gastric mucosal defense mechanisms
- Mechanism of nitric oxide synthesis
- Gastroprotective effects of nitric oxide
- Mechanism of ulcer healing
- Role of nitric oxide in inflammation, angiogenesis, and tissue repair

4.2 Materials Used in Nitric Oxide–Generating Mouth Dissolving Tablets

- Active pharmaceutical ingredients
- Nitric oxide-generating agents
- Acid accelerators
- Superdisintegrants
- Fillers and diluents
- Binders
- Lubricants and glidants
- Sweeteners and flavoring agents
- Antioxidants and stabilizers

Table 4.1. Materials Used in Nitric Oxide–Generating Mouth Dissolving Tablets

Material	Category	Function	Common Concentration
Sodium Nitrite	NO precursor	Nitric oxide generation	2–10%
Citric Acid	Acid accelerator	Initiates NO generation	5–20%
Ascorbic Acid	Antioxidant	Supports NO release	2–10%
Mannitol	Diluent	Improves mouthfeel	20–60%
Croscarmellose Sodium	Superdisintegrant	Rapid disintegration	2–8%
PVP K-30	Binder	Tablet strength	1–5%
Magnesium Stearate	Lubricant	Prevents sticking	0.5–1%
Talc	Glidant	Improves powder flow	1–3%

4.3 Formulation and Manufacturing of Nitric Oxide–Generating Mouth Dissolving Tablets

4.3.1 Formulation

Nitric oxide (NO)-generating mouth dissolving tablets (MDTs) are formulated using the direct compression technique because it is simple, economical, and suitable for moisture- and heat-sensitive ingredients. The formulation consists of a nitric oxide precursor, an acid accelerator, superdisintegrants, diluents, binders, lubricants, and glidants. Sodium nitrite is commonly used as the nitric oxide-generating agent, while citric acid and ascorbic acid facilitate rapid nitric oxide release in the presence of saliva. Mannitol serves as a water-soluble diluent that improves mouthfeel and tablet palatability. Croscarmellose sodium acts as a superdisintegrant to ensure rapid tablet disintegration. Polyvinylpyrrolidone (PVP K-30) provides adequate binding strength, whereas magnesium stearate and talc improve powder flow and prevent sticking during compression. The careful selection and optimization of these excipients ensure rapid disintegration, acceptable mechanical strength, good stability, and enhanced patient compliance.

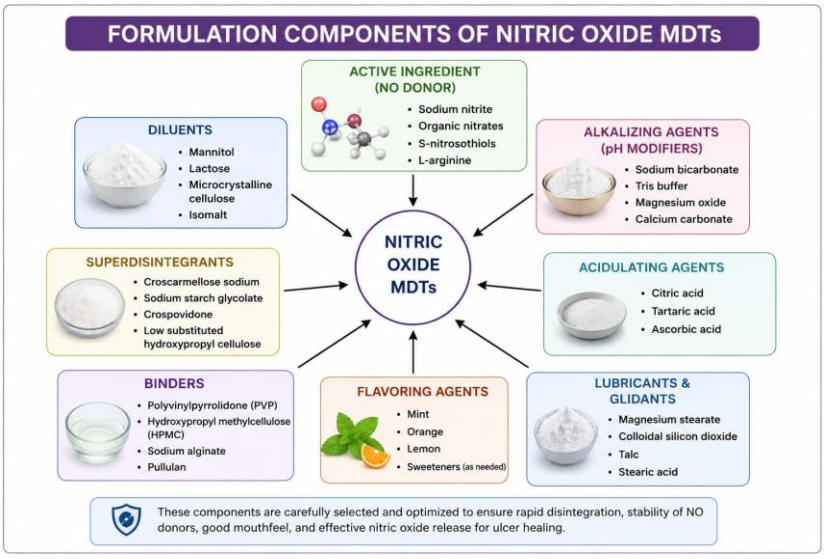


Table 4.3. Formulation Components of Nitric Oxide–Generating MDTs

Ingredient	Category	Function
Sodium Nitrite	Active ingredient	nitric oxide release
Citric Acid	Acid accelerator	Initiates nitric oxide release
Ascorbic Acid	Antioxidant/Acidifier	Enhances NO generation and stability
Mannitol	Diluent	Improves mouthfeel and tablet bulk
Croscarmellose Sodium	Superdisintegrant	Rapid tablet disintegration
PVP K-30	Binder	Provides tablet strength
Magnesium Stearate	Lubricant	Prevents sticking during compression
Talc	Glidant	Improves powder flow

4.3.2 Manufacturing Method

The tablets are generally manufactured by the **direct compression method**, which is widely used for mouth dissolving tablets because of its simplicity and cost-effectiveness. Initially, all ingredients are accurately weighed according to the formulation. The powders are passed through a suitable sieve to obtain uniform particle size and remove aggregates. The active ingredient, nitric oxide precursor, acid accelerator, superdisintegrant, and diluent are blended uniformly to achieve a homogeneous powder mixture. The binder is incorporated to improve compressibility, followed by the addition of lubricants and glidants during the final mixing stage. The lubricated blend is then compressed into tablets using a rotary tablet compression machine under optimized compression force. The compressed tablets are evaluated for physical characteristics, disintegration time, friability, hardness, weight variation, and drug content to ensure compliance with pharmacopeial standards. Finally, the tablets are packed in moisture-resistant packaging materials to protect the nitric oxide-generating components from environmental degradation during storage.

Flow Chart of Manufacturing Process

Raw Materials Selection
↓
Accurate Weighing of Ingredients
↓
Sieving (40–60 Mesh)
↓
Dry Mixing of Active Ingredient,
Acid Accelerator, Diluent and Superdisintegrant
↓
Addition of Binder
↓
Lubrication
(Add Magnesium Stearate and Talc)
↓
Final Blending
↓
Direct Compression
↓
Evaluation of Tablets
(Hardness, Friability, Disintegration,
Weight Variation, Drug Content)
↓
Packaging in Moisture-Proof Containers
↓
Finished Product

4.4 Evaluation Parameters

Pre-compression Evaluation

- Angle of repose
- Bulk density
- Tapped density
- Carr's Index
- Hausner Ratio

Post-compression Evaluation

- Appearance
- Weight variation
- Thickness
- Hardness
- Friability

Specialized Evaluation

- Disintegration time
- Wetting time
- Water absorption ratio
- Drug content uniformity
- Dissolution study
- Stability study

Table 4.2. Evaluation Parameters of Mouth Dissolving Tablets

Evaluation Test	**Purpose**	**Acceptable Limit**
Angle of Repose	Powder flow	<30°
Bulk Density	Packing property	Report value
Tapped Density	Compressibility	Report value
Carr's Index	Flowability	5–15% (Excellent)
Hausner Ratio	Flow property	<1.25
Weight Variation	Dose uniformity	IP limits
Hardness	Mechanical strength	2–4 kg/cm²
Thickness	Tablet uniformity	±5%
Friability	Mechanical resistance	≤1%
Disintegration Time	Tablet breakdown	<60 s (MDTs)
Wetting Time	Water uptake	As low as possible
Drug Content	Uniformity	95–105%
Dissolution	Drug release	As per specification
Stability Study	Shelf life	ICH guidelines

5. Challenges

5.1 Challenges

Despite the promising therapeutic potential of nitric oxide (NO)-generating mouth dissolving tablets (MDTs), several scientific and technological challenges remain. One of the major concerns is maintaining the stability of nitric oxide-generating components during manufacturing and storage. Nitrite-based formulations are sensitive to moisture, heat, and light, which may result in premature degradation and reduced therapeutic efficacy. Therefore, appropriate formulation strategies and moisture-resistant packaging are essential.

Another challenge is achieving controlled and reproducible nitric oxide release. Excessive nitric oxide production may cause oxidative stress and local irritation, whereas insufficient release may reduce gastroprotective activity. Optimization of the acid accelerator system and formulation composition is therefore critical.

MDTs also require a balance between rapid disintegration and adequate mechanical strength. Increasing the concentration of superdisintegrants may shorten disintegration time but can adversely affect tablet hardness and friability. In addition, large-scale industrial manufacturing requires strict process optimization to maintain batch-to-batch consistency and product quality.

5.2 Research Gaps

Although numerous experimental studies have demonstrated the gastroprotective effects of nitric oxide, several important research gaps remain.

- Limited clinical trials evaluating nitric oxide-generating MDTs in human subjects.
- Insufficient long-term safety and toxicity data following repeated administration.
- Lack of comparative studies against currently available anti-ulcer therapies.
- Limited information regarding pharmacokinetics and in vivo nitric oxide release profiles.
- Inadequate investigation of drug–excipient compatibility and formulation stability during long-term storage.
- Few studies evaluating patient acceptability, treatment adherence, and quality-of-life outcomes.
- Limited evidence supporting large-scale manufacturing feasibility and commercial production.
- Need for advanced formulation approaches such as nanotechnology, controlled nitric oxide delivery systems, and personalized oral dosage forms.

Addressing these research gaps will facilitate the successful clinical translation and commercialization of nitric oxide-generating mouth dissolving tablets.

6. Future Scope

Nitric oxide (NO)-generating mouth dissolving tablets (MDTs) represent an emerging approach in oral drug delivery with significant potential for improving the management of peptic ulcer disease. Although encouraging results have been reported in preclinical studies, further scientific advancements are required to translate these formulations into routine clinical practice. Future research should focus on improving formulation stability, achieving controlled nitric oxide release, enhancing therapeutic efficacy, and ensuring long-term patient safety.

6.1 Emerging Technologies

Nanotechnology-Based Drug Delivery

The integration of nanotechnology with nitric oxide-generating systems offers opportunities to improve drug stability, targeted delivery, and bioavailability. Nanocarriers such as polymeric nanoparticles, liposomes, and nanogels can protect nitric oxide precursors from premature degradation while enabling controlled and site-specific release at the gastric mucosa.

Smart and Stimuli-Responsive Delivery Systems

Future formulations may incorporate stimuli-responsive materials capable of releasing nitric oxide in response to specific physiological conditions, including changes in gastric pH, inflammation, or oxidative stress. Such intelligent delivery systems may improve therapeutic precision while minimizing unnecessary nitric oxide exposure.

Three-Dimensional (3D) Printing Technology

Three-dimensional printing has emerged as a promising manufacturing technology for personalized oral dosage forms. The application of 3D printing in MDT development may allow customization of tablet size, drug dose, disintegration time, and nitric oxide release characteristics according to individual patient requirements.

Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning algorithms are increasingly being utilized in pharmaceutical formulation development. These technologies can assist in optimizing excipient selection, predicting formulation performance, reducing experimental workload, and accelerating product development through data-driven decision-making.

Quality by Design (QbD)

Implementation of the Quality by Design approach is expected to enhance formulation robustness by identifying critical material attributes and process parameters that influence product quality. QbD can improve manufacturing consistency, reduce variability, and facilitate regulatory approval.

7. Conclusion

NitroCure mouth dissolving tablets demonstrated satisfactory pharmaceutical characteristics, including good flow, adequate mechanical strength, rapid wetting, and disintegration. The formulation showed promising potential as a convenient and patient-friendly approach for peptic ulcer management through nitric oxide generation. Further optimization, stability studies, and in-vitro and in-vivo investigations are recommended to confirm its therapeutic potential and support future development.

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Abbreviations

Abbreviation	Full Form
AA	Ascorbic Acid
AI	Artificial Intelligence
API	Active Pharmaceutical Ingredient
AOR	Angle of Repose
BD	Bulk Density
CA	Citric Acid
CCS	Croscarmellose Sodium
CI	Carr's Index
CMA	Critical Material Attribute
CPP	Critical Process Parameter
DT	Disintegration Time
FDT	Fast Dissolving Tablet
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GMP	Good Manufacturing Practice
H_2RA	Histamine-2 Receptor Antagonist
H. pylori	*Helicobacter pylori*
HR	Hausner Ratio
ICH	International Council for Harmonisation
IP	Indian Pharmacopoeia
MCC	Microcrystalline Cellulose

Abbreviation	Full Form
MDT	Mouth Dissolving Tablet
Mg Stearate	Magnesium Stearate
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ODT	Orally Disintegrating Tablet
PEG	Polyethylene Glycol
PPI	Proton Pump Inhibitor
PUD	Peptic Ulcer Disease
PVP K-30	Polyvinylpyrrolidone K-30
QA	Quality Assurance
QbD	Quality by Design
QC	Quality Control
RH	Relative Humidity
ROS	Reactive Oxygen Species
SN	Sodium Nitrite
SSG	Sodium Starch Glycolate
TD	Tapped Density
USP	Unique Selling Point
UV	Ultraviolet
WAR	Water Absorption Ratio
WHO	World Health Organization
WT	Wetting Time

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