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Formulation, Development and Evaluation of Immediate-Release Tablets for Anti-Tuberculosis Drugs: A Comprehensive Review

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ABSTRACT

Tuberculosis (TB) remains an important infectious disease and requires effective, accessible and patient-friendly pharmacotherapy. Oral solid dosage forms, particularly immediate-release (IR) tablets, continue to play a major role in the delivery of anti-tuberculosis drugs because of their convenience, stability, portability and suitability for large-scale manufacturing. This review discusses the development, formulation and evaluation of immediate-release tablets containing anti-tuberculosis drugs, with particular emphasis on formulation principles applicable to isoniazid and other first-line agents. The review covers the disease background, commonly used anti-tuberculosis drugs, preformulation considerations, selection of excipients, direct compression and granulation approaches, manufacturing process development, pre-compression and post-compression evaluation, drug–excipient compatibility, dissolution testing, assay and content uniformity, stability studies and quality-by-design considerations. Particular attention is given to critical quality attributes such as powder flow, compressibility, tablet hardness, friability, disintegration, drug content and dissolution. Appropriate formulation and process optimization can improve tablet manufacturability, dose uniformity and drug-release performance while maintaining product quality and stability. The review provides a formulation-oriented framework for the development and evaluation of immediate-release anti-tuberculosis tablets for academic and pharmaceutical research applications.

Keywords

Tuberculosis; Anti-tuberculosis drugs; Isoniazid; Immediate-release tablets; Direct compression; Wet granulation; Preformulation; Dissolution; Drug–excipient compatibility; Quality by Design.

I. INTRODUCTION

Tuberculosis is an infectious disease caused predominantly by Mycobacterium tuberculosis and remains a major global public-health concern. Successful treatment depends on appropriate drug selection, adequate exposure, adherence and maintenance of therapeutic drug concentrations for the prescribed duration. First-line anti-tuberculosis therapy commonly involves combinations of agents such as isoniazid, rifampicin, pyrazinamide and ethambutol. Because treatment may involve multiple medicines and prolonged administration, dosage-form design is important for improving usability and maintaining consistent drug delivery.

Tablets are among the most widely used oral dosage forms because they offer dose accuracy, ease of administration, relatively low manufacturing cost and good physical stability. Immediate-release tablets are designed to disintegrate and release the active pharmaceutical ingredient (API) without intentionally providing modified or prolonged release. For anti-tuberculosis therapy, appropriate IR formulation can support rapid drug availability after oral administration while maintaining acceptable mechanical and chemical quality.

The development of an IR tablet involves systematic evaluation of the API and excipients, selection of a suitable manufacturing method, optimization of formulation variables and evaluation of critical quality attributes. Preformulation studies provide information regarding solubility, particle characteristics, bulk and tapped density, flow, compressibility, pH, moisture sensitivity and compatibility. These data guide excipient selection and manufacturing-process design.

II. TUBERCULOSIS: DISEASE OVERVIEW

Tuberculosis primarily affects the lungs, although extrapulmonary disease can occur. Common clinical manifestations of pulmonary TB include persistent cough, fever, night sweats, fatigue, loss of appetite and weight loss. Diagnosis may involve clinical assessment, microbiological testing, molecular methods and imaging as appropriate. Treatment requires combination

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chemotherapy to improve efficacy and reduce the risk of emergence of drug resistance.

From a formulation perspective, the prolonged therapeutic course and use of multiple anti-TB agents make dosage-form quality particularly important. Consistent dose delivery, rapid and reproducible drug release, acceptable stability and patient acceptability are key considerations in oral tablet development.

III. ANTI-TUBERCULOSIS DRUGS

Drug	Major role	Mechanistic target	Formulation relevance
Isoniazid	First-line therapy	Inhibits mycolic-acid synthesis after activation	Low-dose, potent API; compatibility, content uniformity and dissolution are important.
Rifampicin	First-line therapy	Inhibits bacterial DNA-dependent RNA polymerase	Dose, stability, solubility and drug-release behavior require careful control.
Pyrazinamide	First-line therapy	Active against susceptible bacilli under acidic conditions	High dose can influence tablet size, compressibility and manufacturability.
Ethambutol	First-line therapy	Interferes with mycobacterial cell-wall-related processes	Dose uniformity, tablet dimensions and mechanical properties are important.

IV. IMMEDIATE-RELEASE TABLETS AS ORAL DOSAGE FORMS

Immediate-release tablets are conventional solid dosage forms intended to disintegrate promptly after administration and make the drug available for dissolution and absorption. Their performance depends on tablet composition, compression force, porosity, disintegration behavior, API properties and dissolution characteristics.

Advantages

- Convenient administration and portability.
- Good dose accuracy and reproducibility.
- Relatively simple large-scale manufacturing.
- Good physical stability compared with many liquid dosage forms.
- Potential for rapid disintegration and drug release when appropriately formulated.

Limitations

- Some APIs may have poor aqueous solubility or unfavorable dissolution.
- Poor powder flow can affect die filling and dose uniformity.
- High compression force may reduce porosity and slow disintegration.
- Moisture, heat or chemical incompatibility may affect stability.

V. PREFORMULATION STUDIES

Preformulation establishes the physicochemical and biopharmaceutical profile of the API before formulation development. Important studies include description, particle size, solubility, pH-related behavior, bulk density, tapped density, angle of repose, Carr's compressibility index, Hausner ratio, moisture-related characteristics and compatibility with selected excipients.

Parameter	Purpose	Formulation implication
Bulk density	Determines bulk volume and packing behavior	Helps estimate blend volume and hopper/die behavior.
Tapped density	Assesses packing after tapping	Used with bulk density for flow/compressibility indices.
Carr's index	Indicates compressibility/flow	Lower values generally indicate better flow.
Hausner ratio	Assesses interparticle friction/flow	Values closer to 1 generally

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		indicate better flow.
Angle of repose	Evaluates powder flow	Lower angle generally indicates better flow.
Solubility	Assesses drug dissolution potential	Guides formulation and dissolution optimization.
Drug–excipient compatibility	Detects possible interactions	Supports rational excipient selection.

VI. FORMULATION STRATEGIES

6.1 Direct Compression

Direct compression involves blending the API with suitable excipients followed by compression into tablets. It is attractive because it requires fewer processing steps and avoids exposure to granulation liquids. The approach is most suitable when the formulation blend demonstrates acceptable flow, compressibility and content uniformity.

6.2 Wet Granulation

Wet granulation converts powder mixtures into granules using a granulating liquid and subsequent drying. It can improve flow, reduce segregation and enhance compressibility, but requires additional processing and control of moisture and drying conditions.

6.3 Dry Granulation

Dry granulation uses compaction or slugging/roller compaction without a liquid binder. It can be useful for moisture-sensitive materials and reduces the need for a drying step.

VII. EXCIPIENT SELECTION

Excipient category	Examples	Function
Diluent	Microcrystalline cellulose, lactose, mannitol	Provides bulk and improves compression.
Binder	Povidone, starch derivatives	Improves particle adhesion and granule strength.
Disintegrant	Croscarmellose sodium, crospovidone, sodium starch glycolate	Promotes tablet breakup and drug release.
Glidant	Colloidal silicon dioxide	Improves powder flow.
Lubricant	Magnesium stearate, stearic acid	Reduces friction during compression/ejection.
Antiadherent	Talc	Reduces sticking and picking.

VIII. MANUFACTURING PROCESS DEVELOPMENT

A typical IR tablet development workflow includes dispensing and sieving of materials, geometric dilution or ordered blending where appropriate, lubrication, compression and in-process quality checks. Process parameters such as blending time, lubricant concentration, compression force, turret speed, fill depth and environmental conditions may influence final tablet quality.

Process development should aim to obtain a uniform blend without excessive segregation or over-lubrication. Compression conditions should produce tablets with adequate mechanical strength while preserving sufficient porosity for rapid disintegration and dissolution.

IX. PRE-COMPRESSION EVALUATION

The powder blend is evaluated before compression to determine its suitability for tablet manufacturing. Common tests include angle of repose, bulk density, tapped density, Carr's index, Hausner ratio and particle-size distribution. These parameters help identify flow and packing characteristics and support optimization of the formulation.

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X. POST-COMPRESSION EVALUATION

Test	Purpose	Typical interpretation
Appearance	Checks visual quality	Tablets should be uniform and free from defects.
Weight variation	Assesses consistency of tablet mass	Should comply with applicable pharmacopoeial requirements.
Thickness/diameter	Controls physical dimensions	Supports process consistency and packaging suitability.
Hardness	Measures resistance to crushing	Adequate strength is needed without compromising disintegration.
Friability	Measures resistance to abrasion	Low friability indicates acceptable mechanical integrity.
Disintegration	Measures tablet breakup	IR tablets should disintegrate within the applicable specification.
Assay	Determines drug content	Should comply with the relevant specification.
Content uniformity	Assesses unit-to-unit dose consistency	Important especially for potent or low-dose APIs.
Dissolution	Measures drug release into dissolution medium	Should meet the predefined release specification.

XI. DISSOLUTION STUDIES

Dissolution testing evaluates the rate and extent of drug release from the tablet under standardized in-vitro conditions. Selection of dissolution apparatus, medium, volume, temperature, agitation speed and sampling intervals should be justified for the drug and formulation. A dissolution profile can be used to compare formulations and identify the effect of excipient type, concentration, compression force and manufacturing method.

For an IR product, rapid and reproducible release is generally desirable, subject to the drug-specific monograph or product specification. Dissolution data should be interpreted together with disintegration, hardness, friability and assay results rather than as an isolated parameter.

XII. DRUG–EXCIPIENT COMPATIBILITY

Compatibility studies are conducted to identify physical or chemical interactions between the API and excipients. Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), thermogravimetric analysis and other suitable techniques may be used depending on the development objective. A compatibility study should compare the API, individual excipients and representative mixtures and should assess whether important characteristic peaks or thermal events are altered.

XIII. ANALYTICAL EVALUATION

Quantitative analysis may be performed using a validated UV-visible spectrophotometric or chromatographic method, depending on the analytical characteristics of the API and formulation. The method should be suitable for the intended purpose and appropriately assessed for parameters such as specificity, linearity, accuracy, precision, range and robustness where applicable.

XIV. STABILITY STUDIES

Stability testing evaluates whether the formulation maintains acceptable quality throughout the proposed storage period. Relevant attributes may include appearance, assay, degradation products, dissolution, hardness, friability and moisture. Stability conditions and study design should follow the applicable regulatory and pharmacopoeial expectations for the intended product and market.

XV. QUALITY BY DESIGN APPROACH

Quality by Design (QbD) provides a systematic framework for understanding formulation and process variables that can affect product performance. The development process can begin with a quality target product profile (QTPP), followed by identification of critical quality

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attributes (CQAs), critical material attributes (CMAs) and critical process parameters (CPPs). Risk assessment and design-of-experiments approaches can then be used to optimize the formulation and establish an appropriate control strategy.

Development element	Example for IR anti-TB tablet
QTPP	Immediate-release oral tablet with consistent dose and acceptable stability.
CQAs	Assay, content uniformity, hardness, friability, disintegration and dissolution.
CMAs	API particle size, excipient grade and moisture content.
CPPs	Blending time, lubrication time, compression force and machine speed.
Control strategy	Raw-material controls, in-process testing and finished-product specifications.

XVI. FACTORS AFFECTING DRUG RELEASE

Drug release from IR tablets is affected by API solubility, particle size, crystal form, wettability, dose, excipient type and concentration, disintegrant efficiency, binder level, lubricant concentration, compression force, tablet porosity and manufacturing method. Higher compression can increase tablet strength but may reduce porosity and delay liquid penetration and disintegration. Hydrophobic lubricant overuse may also adversely affect wetting and dissolution.

The relationship between formulation variables and disintegration is complex. Recent research indicates that raw-material characteristics, compression settings and tablet microstructure can interact to determine final disintegration and dissolution behaviour. [1]

XVII. RECENT FORMULATION DEVELOPMENTS

Recent pharmaceutical development increasingly emphasizes patient-centered dosage forms, process understanding, improved dissolution performance and robust manufacturing. For anti-tuberculosis therapy, formulation development may also consider fixed-dose combinations, dose burden, stability, manufacturability and adherence. Modern approaches can include optimized excipient combinations, particle engineering, solid-state modification, enhanced dissolution technologies and QbD-guided process optimization where justified by the properties of the API.

XVIII. CHALLENGES AND FUTURE PERSPECTIVES

- Achieving adequate dissolution for APIs with unfavorable aqueous solubility.
- Maintaining content uniformity when formulation doses are low or powders have different densities and particle sizes.
- Balancing tablet hardness with rapid disintegration and dissolution.
- Controlling moisture and chemical stability during manufacturing and storage.
- Developing robust processes that remain reproducible during scale-up.
- Using QbD and risk-based approaches to improve formulation understanding and control.

XIX. CONCLUSION

Development of immediate-release tablets for anti-tuberculosis drugs requires an integrated understanding of API properties, excipient functionality, manufacturing processes and product-performance requirements. Preformulation studies provide the foundation for rational formulation design, while selection of direct compression, wet granulation or dry granulation should be based on the material and process characteristics. Evaluation of powder flow, tablet physical properties, assay, content uniformity, disintegration and dissolution provides evidence of formulation quality. Compatibility and stability studies further support the suitability of the developed product. A systematic QbD-based approach can strengthen process understanding and help identify critical formulation and manufacturing variables. Overall, optimized immediate-release tablet formulations can provide reproducible drug delivery, acceptable manufacturability and a practical oral dosage form for anti-tuberculosis therapy.

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