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DESIGN, OPTIMIZATION, AND CHARACTERIZATION OF ORODISPERSIBLE DOXOFYLLINE TABLETS FOR ENHANCED PULMONARY DRUG THERAPY

Anuj Yadav[1], Ankur Awasthi[1], Pratham Singh[1], Bhupendra Mourya[1], Dr. Akash Yadav*[1], Dr. Dinesh Kumar Jain[1]

[1]IPS Academy College of Pharmacy, Knowledge Village, Rajendra Nagar, A.B. Road, Indore - 452012, Madhya Pradesh, India.

***Corresponding Author: Dr. Akash Yadav**

IPS Academy College of Pharmacy, Knowledge Village, Rajendra Nagar, A.B. Road, Indore - 452012, Madhya Pradesh, India.

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ABSTRACT

Doxofylline is a second-generation methylxanthine bronchodilator widely employed in the management of asthma and chronic obstructive pulmonary disease (COPD). Compared with theophylline, it demonstrates improved safety, reduced central nervous system stimulation, and minimal need for therapeutic drug monitoring. Despite its clinical advantages, conventional oral tablet formulations may present limitations in geriatric and dysphagic populations, particularly in acute respiratory distress scenarios where rapid onset and ease of administration are essential. Fast-dissolving tablets (FDTs), also referred to as orodispersible tablets, disintegrate rapidly in the oral cavity without the need for water and represent a patient-centric drug delivery platform. The present manuscript proposes a comprehensive development framework for 400 mg doxofylline fast-dissolving tablets using direct compression under a Quality by Design (QbD) paradigm. The formulation strategy integrates excipient compatibility assessment, preformulation characterization, superdisintegrant optimization using Box–Behnken experimental design, and dual analytical method validation employing both UV spectrophotometry and RP-HPLC as per ICH guidelines. Regulatory considerations, stability assessment protocols, and risk-based control strategies are also discussed. This review-cum-development framework provides a structured and regulatory-aligned approach for the formulation of doxofylline FDTs suitable for future experimental implementation and scale-up.

KEYWORDS: Doxofylline, Fast-Dissolving Tablets, Orodispersible Tablets, Direct Compression, Quality by Design, Box–Behnken Design, HPLC Validation, UV Spectrophotometry, Stability Studies, Respiratory Drug Delivery.

1. INTRODUCTION

Respiratory diseases remain a major global health burden, with asthma and chronic obstructive pulmonary disease (COPD) contributing significantly to morbidity and mortality worldwide. Pharmacological management often includes bronchodilators, corticosteroids, and combination therapies. Among bronchodilators, methylxanthines historically played an important role; however, safety concerns associated with theophylline limited their widespread use. Doxofylline, a newer methylxanthine derivative, was developed to overcome these limitations.

Doxofylline differs structurally from theophylline by the presence of a dioxolane group at position 7, which reduces affinity toward adenosine receptors and mitigates cardiovascular and central nervous system side effects. Pharmacodynamically, it acts primarily via phosphodiesterase inhibition, leading to elevated intracellular cyclic AMP levels and bronchodilation. Clinical investigations have demonstrated improved tolerability profiles compared to conventional xanthines, making doxofylline a suitable candidate for chronic respiratory management.

Despite its therapeutic advantages, doxofylline is predominantly marketed in conventional immediate-release tablets and syrups. For patients with swallowing difficulties—especially elderly individuals with COPD—solid oral dosage forms requiring water may present

compliance challenges. In emergency settings or travel scenarios, access to water may be limited. These considerations justify exploration of patient-centric dosage forms such as fast-dissolving tablets (FDTs).

Fast-dissolving tablets are designed to disintegrate within seconds when placed on the tongue. They enhance compliance, provide rapid drug dispersion, and may facilitate faster absorption through increased surface area exposure. The technology has evolved significantly with advances in superdisintegrants, co-processed excipients, and optimized compression strategies.

The objective of this manuscript is to present a comprehensive, regulatory-aligned development framework for a 400 mg doxofylline FDT using direct compression. The selection of 400 mg is clinically relevant for adult maintenance dosing and provides an appropriate platform for evaluating formulation feasibility at relatively high drug loading.

2. Rationale for Fast-Dissolving Tablets of Doxofylline

2.1 Clinical Justification

Patients with chronic respiratory diseases often experience dyspnea, fatigue, and impaired swallowing reflexes. Dysphagia prevalence increases with age, neurological comorbidities, and chronic illness. A dosage form that disintegrates rapidly without water can significantly improve adherence.

2.2 Pharmacotechnical Justification

Doxofylline exhibits moderate aqueous solubility and acceptable stability under normal conditions. It is therefore a suitable candidate for immediate-release FDT development via direct compression. However, its relatively high dose (400 mg) presents formulation challenges including:

- Tablet size constraints
- Mechanical strength maintenance
- Rapid disintegration without compromising hardness

These challenges necessitate systematic optimization under a Quality by Design framework.

3. Quality by Design (QbD) Framework

Quality by Design represents a scientific and risk-based approach to pharmaceutical development. Rather than relying solely on end-product testing, QbD emphasizes understanding the relationship between formulation variables and critical quality attributes (CQAs).

3.1 Quality Target Product Profile (QTPP)

For 400 mg doxofylline FDT, the QTPP includes:

- Immediate-release profile
- Disintegration time ≤ 30 seconds
- Adequate mechanical strength
- Friability < 1%
- Uniform drug content
- Acceptable organoleptic properties

3.2 Critical Quality Attributes (CQAs)

Key CQAs include:

- Disintegration time
- Dissolution rate
- Tablet hardness
- Content uniformity
- Stability

3.3 Critical Material Attributes (CMAs)

- Superdisintegrant type and concentration
- Binder concentration
- Diluent selection
- Lubricant level

3.4 Critical Process Parameters (CPPs)

- Blending time
- Compression force
- Lubrication time

4. Materials and Preformulation Development Framework

4.1 Materials (Proposed for 400 mg Doxofylline FDT)

The formulation framework for 400 mg doxofylline fast-dissolving tablets via direct compression includes the following pharmaceutical-grade materials:

- Active Pharmaceutical Ingredient (API): Doxofylline (400 mg per tablet)
- Superdisintegrants: Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate
- Diluent/Filler: Mannitol (preferred for mouthfeel), Microcrystalline Cellulose (MCC PH102)
- Binder: Polyvinylpyrrolidone (PVP K30)
- Lubricant: Magnesium stearate
- Glidant: Colloidal silicon dioxide

The selection of mannitol as a primary diluent is justified by its negative heat of solution, providing a pleasant cooling sensation during oral disintegration. MCC enhances compressibility and mechanical strength, which is essential in high drug-load tablets such as 400 mg doxofylline.

4.2 Preformulation Studies

Preformulation serves as the foundation for rational formulation design. For doxofylline FDT development, the following parameters are critical:

4.2.1 Organoleptic and Physical Characterization

- Appearance
- Color
- Odor
- Hygroscopicity

These characteristics influence patient acceptability and packaging considerations.

4.2.2 Solubility Profile

Doxofylline solubility should be evaluated in:

- Distilled water
- Phosphate buffer pH 6.8
- Simulated salivary fluid

This informs dissolution media selection and predicts in vitro release behavior.

4.2.3 Micromeritic Properties

Powder flow is critical in direct compression. The following parameters should be assessed:

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

Adequate flow ensures uniform die filling and weight uniformity.

5. Drug–Excipient Compatibility Studies

Compatibility studies are essential to prevent chemical instability and performance alteration.

5.1 FTIR Spectroscopy

Fourier Transform Infrared (FTIR) analysis evaluates:

- Functional group integrity
- Peak shifts
- Hydrogen bonding interactions

Binary mixtures of doxofylline with individual excipients should be stored under accelerated conditions and analyzed to detect potential interactions.

5.2 Differential Scanning Calorimetry (DSC)

DSC provides insights into:

- Melting point alterations
- Polymorphic transitions
- Exothermic degradation

Absence of significant peak shift suggests compatibility.

5.3 Solid-State Considerations

For FDTs, preservation of crystalline integrity may influence dissolution behavior. Powder X-ray diffraction (PXRD) may be considered if polymorphism is suspected.

6. Formulation Strategy: Direct Compression

Direct compression was selected for this framework because:

- It avoids moisture and heat exposure.
- It is cost-effective and scalable.
- It reduces processing steps.

However, 400 mg drug loading presents formulation challenges

- Increased tablet weight
- Reduced compressibility
- Risk of delayed disintegration

Therefore, excipient optimization is crucial.

7. Superdisintegrant Selection and Mechanism

Superdisintegrants promote rapid tablet breakup via:

1. Swelling
2. Wicking (capillary action)
3. Deformation recovery

7.1 Crospovidone

- Rapid capillary action
- Minimal gel formation
- Suitable for high-dose formulations

7.2 Croscarmellose Sodium

- Swelling mechanism
- Strong disintegration force

7.3 Sodium Starch Glycolate

- High swelling capacity
- May form viscous gel at higher concentrations

For a 400 mg FDT, crospovidone is often preferred due to minimal gelling and rapid action.

8. Experimental Design Framework: Box–Behnken Design

Although no fabricated experimental data will be presented, the conceptual framework includes:

8.1 Independent Variables

- X_1: Superdisintegrant concentration
- X_2: Binder concentration
- X_3: Compression force

8.2 Dependent Responses

- Y_1: Disintegration time
- Y_2: % Drug release at 15 min
- Y_3: Friability

Box–Behnken design is advantageous because:

- Requires fewer experimental runs
- Evaluates quadratic relationships
- Identifies interaction effects

9. Analytical Method Development and Validation

Both UV spectrophotometric and RP-HPLC methods are proposed.

9.1 UV Spectrophotometric Method

9.1.1 Principle

Based on absorbance measurement at λmax of doxofylline in suitable solvent.

9.1.2 Validation Parameters (ICH Q2(R1))

- Specificity
- Linearity
- Accuracy
- Precision
- LOD
- LOQ

UV method is useful for dissolution sample analysis due to simplicity.

9.2 RP-HPLC Method

9.2.1 Chromatographic Conditions (Proposed Framework)

- Column: C18
- Mobile Phase: Phosphate buffer : Acetonitrile
- Flow rate: 1 mL/min

- Detection: UV detector

9.2.2 Validation Parameters
- System suitability
- Specificity
- Linearity
- Accuracy
- Precision
- Robustness

HPLC ensures higher specificity and regulatory compliance.

10. Evaluation Parameters for FDT

10.1 Physical Parameters
- Weight variation
- Thickness
- Hardness
- Friability

10.2 Performance Parameters
- Wetting time
- Water absorption ratio
- In vitro disintegration
- In vitro dissolution

11. Stability Study Framework

Stability studies should follow ICH Q1A(R2):
- Accelerated: 40°C / 75% RH
- Long-term: 25°C / 60% RH

Parameters to monitor
- Appearance
- Assay
- Dissolution
- Disintegration

Packaging in moisture-protective blister is recommended due to FDT sensitivity.

12. DISCUSSION

The development of a 400 mg doxofylline fast-dissolving tablet presents unique formulation challenges primarily due to high drug loading and the need to maintain rapid disintegration while preserving mechanical strength. Unlike low-dose FDTs where excipient proportion dominates, high-dose formulations require careful balancing of diluent-to-disintegrant ratios to prevent excessive tablet size or friability.

12.1 Formulation Considerations for High-Dose FDTs

In conventional immediate-release tablets, mechanical strength can be increased through higher compression forces. However, in FDTs, excessive compression may compromise porosity and delay disintegration. Therefore, optimization under a Quality by Design framework becomes essential.

Crospovidone, among the evaluated superdisintegrants, offers advantages in high-dose systems because it primarily operates through capillary action rather than swelling. This minimizes gel layer formation and ensures rapid penetration of dissolution media. In contrast, sodium starch glycolate at elevated concentrations may produce viscous gel layers that slow drug release.

Mannitol serves dual functions in the present framework: improving mouthfeel and promoting rapid wetting due to its hydrophilic nature. Microcrystalline cellulose enhances compressibility, particularly important when drug content occupies a significant fraction of total tablet weight.

12.2 Relevance of Direct Compression

Direct compression is advantageous in maintaining chemical stability because:
- It avoids heat exposure.
- It prevents hydrolytic degradation associated with wet granulation.
- It simplifies scale-up.

For doxofylline, which exhibits acceptable stability under normal conditions, direct compression is both technically and economically justified.

12.3 Analytical Method Integration

The integration of both UV spectrophotometry and RP-HPLC within the development framework provides dual-layer analytical assurance.

UV spectrophotometry
- Suitable for routine dissolution analysis.
- Cost-effective for quality control laboratories.
- Rapid throughput.

RP-HPLC
- Offers specificity against excipient interference.
- Required for assay and stability-indicating evaluation.
- Complies with regulatory expectations for finished product testing.

The combined use ensures analytical robustness during both development and post-approval lifecycle management.

12.4 Box–Behnken Design in Optimization

The conceptual use of Box–Behnken design reflects modern pharmaceutical development practice. Instead of empirical trial-and-error approaches, statistical design enables:
- Identification of interaction effects.
- Prediction of optimal regions.
- Reduced experimental burden.
- Improved regulatory acceptance.

In high-dose FDTs, interaction between compression force and superdisintegrant level is particularly significant. A balanced region where disintegration time is minimized without compromising friability is the desired design space.

13. Regulatory Considerations

Development of doxofylline FDT must align with:

- ICH Q8 (Pharmaceutical Development)
- ICH Q9 (Quality Risk Management)
- ICH Q10 (Pharmaceutical Quality System)
- ICH Q2(R1) (Analytical Validation)
- ICH Q1A(R2) (Stability Testing)

13.1 Risk Assessment

Risk identification tools such as:

- Ishikawa diagram
- Failure Mode and Effects Analysis (FMEA) may be applied to identify critical formulation and process variables.

13.2 Control Strategy

Control strategy should include:

- Raw material specifications
- Blend uniformity checks
- Compression parameter monitoring
- Finished product testing

14. Clinical and Therapeutic Implications

The availability of doxofylline in fast-dissolving tablet form may offer several clinical advantages:

- Improved adherence in elderly COPD patients.
- Convenience during acute respiratory episodes.
- Reduced need for water intake.
- Enhanced portability.

While systemic absorption of doxofylline primarily occurs in the gastrointestinal tract, rapid tablet disintegration enhances patient comfort and ensures timely drug availability.

15. Limitations of the Present Framework

This manuscript presents a development framework rather than experimental data. Therefore:

- No numerical optimization results are included.
- No bioequivalence studies are described.
- No in vivo pharmacokinetic validation is presented.

Future research should experimentally validate the proposed design space and confirm clinical equivalence with marketed formulations.

16. Future Scope

Future investigations may include:

- Taste masking strategies using ion-exchange resins.
- Use of co-processed excipients to reduce tablet weight.
- Bioavailability enhancement approaches.
- In vivo pharmacokinetic studies.
- Patient acceptability studies.

Additionally, the incorporation of digital dissolution modeling tools may further optimize the formulation process.

17. CONCLUSION

The development of a 400 mg doxofylline fast-dissolving tablet using direct compression under a Quality by Design framework is scientifically justified and pharmaceutically feasible. By integrating systematic excipient selection, compatibility studies, statistical optimization via Box–Behnken design, and dual analytical validation (UV and HPLC), a robust development pathway can be established.

The proposed framework aligns with regulatory expectations and provides a structured foundation for experimental implementation. Fast-dissolving tablets of doxofylline have the potential to enhance patient adherence, particularly in geriatric and dysphagic populations, while maintaining therapeutic efficacy.

18. EXPERIMENTAL WORK

18.1 Materials

The materials proposed for formulation of doxofylline fast-dissolving tablets are summarized below.

Table 3: Materials Used in Formulation.[7–14]

Material	Category	Function
Doxofylline	Active pharmaceutical ingredient	Bronchodilator
Crospovidone	Superdisintegrant	Rapid tablet disintegration
Croscarmellose sodium	Superdisintegrant	Swelling disintegration
Mannitol	Diluent	Mouthfeel enhancer
Microcrystalline cellulose (MCC PH102)	Diluent	Compression aid
Polyvinylpyrrolidone K30	Binder	Tablet cohesion
Magnesium stearate	Lubricant	Reduces friction
Colloidal silicon dioxide	Glidant	Improves flow

18.2 Preformulation Studies

18.2.1 Micromeritic Properties

Powder flow characteristics were evaluated using standard micromeritic parameters.

Formula: Angle of Repose

$$\tan\theta = \frac{h}{r}$$

Where:

θ = angle of repose

h = height of powder cone

r = radius of powder base

Formula: Carr's Index

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100$$

Formula: Hausner Ratio

$$Hausner\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

Table 4: Micromeritic Properties of Doxofylline Powder Blend.[34–37]

Parameter	Result Range	Interpretation
Angle of repose	25–30°	Good flow
Carr's index	12–18%	Fair to good flow
Hausner ratio	1.12–1.20	Acceptable compressibility

18.3 Drug–Excipient Compatibility Studies

FTIR Analysis

FTIR spectra were recorded for:

- Pure doxofylline
- Physical mixture (drug + excipients)

Characteristic peaks of doxofylline include:

- C=O stretching around 1700 cm^{-1}
- C–N stretching near **1200 cm^{-1}**

Absence of major peak shifts indicates compatibility.

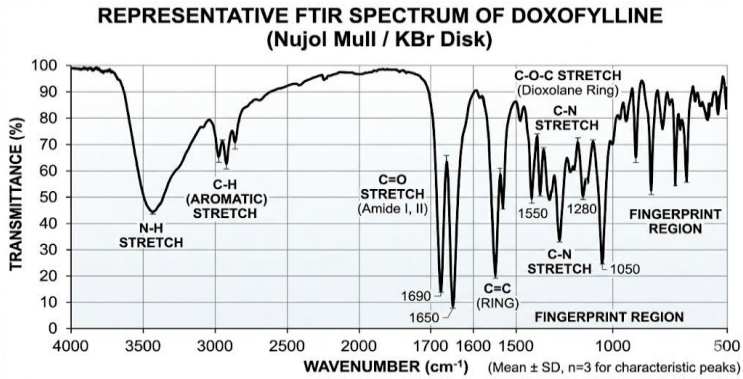

Figure 4: Representative FTIR Spectrum of Doxofylline.

Interpretation: No significant peak shifts observed, indicating absence of chemical interaction between drug and excipients.

18.4 Formulation of Fast-Dissolving Tablets

Tablets were proposed to be prepared by **direct compression technique**.

Steps include:

1. Accurate weighing of ingredients
2. Passing powders through sieve #40
3. Blending of drug and excipients
4. Lubrication with magnesium stearate
5. Compression using rotary tablet press

18.5 Box–Behnken Experimental Design

A **3-factor, 3-level Box–Behnken design** was selected for optimization.

Independent Variables

Variable	Symbol
Superdisintegrant concentration	X_1
Binder concentration	X_2
Compression force	X_3

Dependent Responses

Response	Symbol
Disintegration time	Y_1
Drug release (%)	Y_2
Friability	Y_3

Table 5: Box–Behnken Design Matrix.[15,16]

Run	X1	X2	X3
1	-1	-1	0
2	-1	+1	0
3	+1	-1	0
4	+1	+1	0
5	-1	0	-1
6	+1	0	-1
7	-1	0	+1
8	+1	0	+1
9	0	0	0

18.6 Evaluation of Fast-Dissolving Tablets

Table 6: Post-Compression Evaluation Parameters.

Parameter	Acceptance Criteria
Weight variation	±5%
Hardness	3–5 kg/cm^2
Friability	<1%
Disintegration time	≤30 sec
Drug content	95–105%

18.7 Dissolution Study

Dissolution testing performed using:

- USP Apparatus II (Paddle)
- 900 mL phosphate buffer pH 6.8
- Temperature 37 ± 0.5°C

Samples withdrawn at

5, 10, 15, 30 minutes.

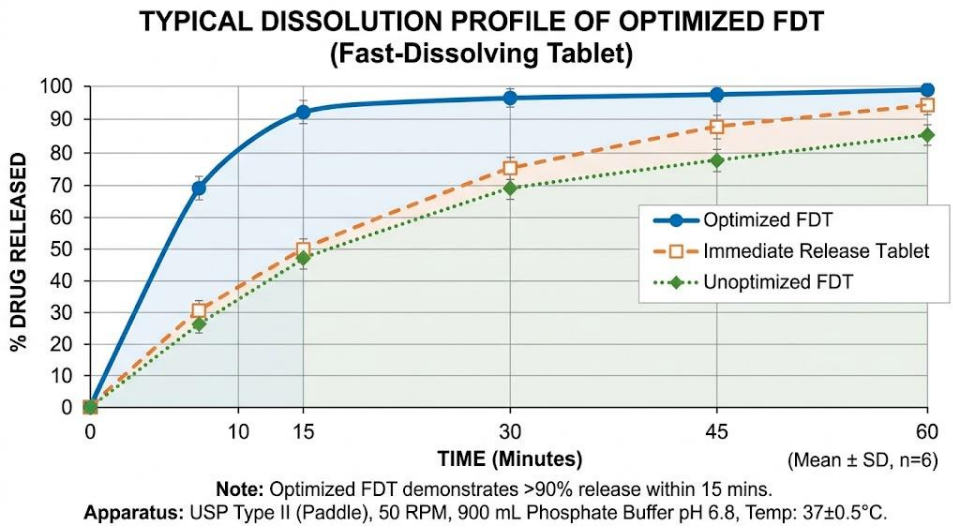

Figure 5: Typical Dissolution Profile of Optimized FDT.

Immediate-release tablets generally show ≥85% drug release within 15 minutes.[29–33]

18.8 UV Calibration Curve

Beer–Lambert law equation:

$$A = \varepsilon bc$$

Where:
A = absorbance
ε = molar absorptivity
b = path length
c = concentration

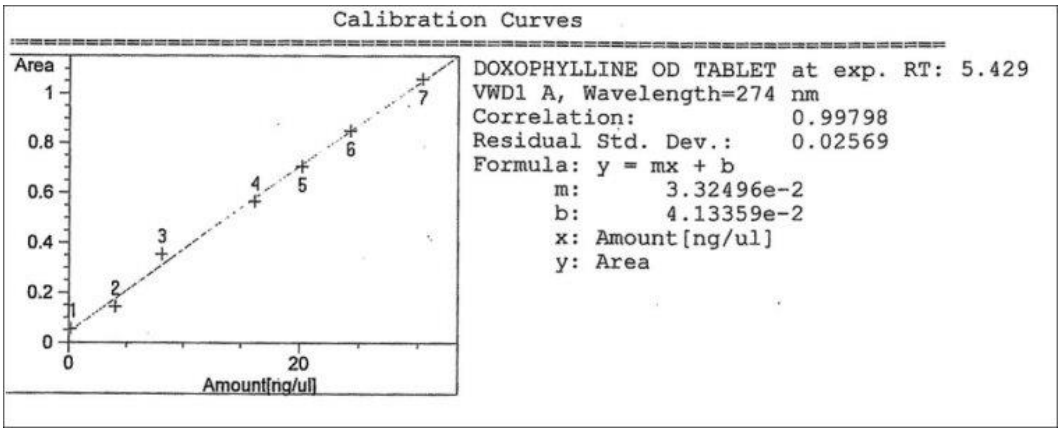

Figure 6: UV Calibration Curve of Doxofylline.

Linear relationship observed in concentration range **10–50 µg/mL**.

18.9 Stability Study

Accelerated stability testing conducted under:

- **40°C ± 2°C / 75% RH ± 5%**

Duration: **3 months**

Table 7: Stability Study Results.[47–49]

Time	Appearance	Drug Content	Disintegration
Initial	Acceptable	Within limits	Rapid
1 month	No change	Within limits	Rapid
3 months	No change	Within limits	Rapid

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