"Development, Optimization and Evaluation of Immediate Release Tablet of Anti-hypertensive Drug Using Concept of Quality by Design"

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in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY
IN
PHARMACEUTICAL TECHNOLOGY & BIOPHARMACEUTICS

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CERTIFICATE

This is to certify that the dissertation work entitled "Development, Optimization and Evaluation of Immediate Release Tablet of Anti-hypertensive Drug Using Concept Of Quality by Design" with Regn. No. (13MPH119) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University and at Formulation development department, Intas Pharmaceuticals Ltd., under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Industrial Guide	**Academic Guide**
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Date: 24 May, 2015

DECLARATION

I hereby declare that the dissertation entitled " Development, Optimization and Evaluation of Immediate Release Tablet of Anti-hypertensive Drug Using Concept Of Quality by Design" is based on the original work carried out by me under the guidance of Dr. Pavan kumar, Senior General Manager, Formulation development department, Intas Pharmaceuticals Ltd., And Prof.Tejal Mehta,Professor & Head,Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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LIST OF ABBREVIATIONS

RLD	Reference Listed Drug
QbD	Quality by Design
QTPP	Quality Target Product Profile
CQAs	Critical Quality Attributes
DoE	Design of Experiments
AR. No	Analytical Report Number.
OGD	Office of Generic Drugs
BE	Bioequivalent
BCS	Biological Classification system
Sr. No	Serial Number
Qty/tab	Quantity per tablet
Mg	Milligram
HDPE	High Density Polyethylene
LOD	Loss on drying
Avg.	Average
HPMC	Hydroxy Propyl Methyl Cellulose
PAR	Proven Acceptable Ranges
RSM	Response Surface Methodology

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ABSTRACT

Development, Optimization and Evaluation of Immediate Release Tablet of Anti-hypertensive Drug Using Concept of Quality by Design

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The present experimental work deals with the systematic quality by design (QbD) based development of DM01 immediate release tablet for treatment for hypertension. The quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD (Reference listed drug) product, pre -formulation study and literature. Identification of critical quality attributes (CQAs) was based on the safety & efficacy, Moreover; risk assessment was carried out throughout development to identify potentially high risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding. Each risk assessment was then updated after development and its level was reduced. Two methods were tried namely direct compression and wet granulation by RMG (rapid mixture granulator) However, wet granulation method was selected based on the drug substance characteristics and release profile to achieve desired QTPP. Optimization of formulation was done using design of experiment (DoE), in which Box-behnken design was used..Impact of change of critical formulation factors on dissolution and disintegration was investigated. Critical process optimization studies were conducted to established consistency of process within targeted ranges. A control strategy was derived that includes the material attributes and process parameters identified as potentially high risk variables during the initial risk assessment. In conclusion, development of immediate release tablet of anti-hypertensive drug DM01 using QbD provides robust, cost effective and industrially applicable formulation in short period of time.

1. AIM OF PRESENT INVESTIGATION

Aim: The aim of present study was to develop & optimize an immediate release dosage form of anti-hypertensive drug (DM01),imbibing the systematic concept of Quality by Design(QbD), with the aid of suitable excipients and evaluating the formulation characteristics.

Strength of selected drug was 40 mg/tablet. The formulation of DM01 for effective oral administration to a subject had been complicated due to unique physical and chemical properties of the compound, particularly its low solubility and factors associated with its low bulk density and low compressibility. DM01 was almost insoluble in aqueous media. Unformulated DM01 is a pro-drug completely hydrolysed in gastrointestinal tract giving the active moiety. It is not readily dissolved and dispersed for its absorption in the gastrointestinal tract when administered orally. Further, handling problems were encountered during the preparation of pharmaceutical compositions comprising DM01. The low bulk density of DM01 made it difficult to process the small quantities required during formulation of the pharmaceutical compositions. Accordingly, there was a need to solve the numerous problems associated with preparation of suitable pharmaceutical compositions and dosage forms comprising DM01, particularly orally deliverable dose units. In particular, a need exists for orally deliverable DM01 formulation using QbD approach possessing one or more of the following characteristics relative to unformulated DM01 or other DM01 compositions: improved solubility; improved compressibility; improved physical stability of the finished composition; better process understanding; quality building in the product by QbD; systematic optimization; better risk assessment.

As indicated here below, DM01 treatment is potentially indicated alone as well as in combination for various types of hypertension i.e. mild, moderate or severe. It would therefore be of great benefit to provide a formulation having bioavailability characteristics tailored to required indication. It would be of special benefit to provide formulation exhibiting consistent with a DM01 onset effect and a better release profile than is possible with unformulated DM01.Such formulation would represent a significant advance in the treatment of hypertension.

Thus, the present study was aimed to formulate the immediate release tablet dosage form of angiotensin receptor blocker(ARB) (BCS class II drug) using the systematic concept of QbD(quality by design) inculcating various process which improve solubility and thereby giving similar bioavailability to RLD(reference listed drug).

OBECTIVES

The main objective of the work is to develop a stable and efficacious immediate release tablet of the given drug by a QbD based approach which includes:

1.Selection of QTTP's and CQA's

2. Pre-formulation studies.

3. Selection of strategy for formulation.

4. Risk assessment.

5. Optimizing the formulation using DoE.

6. Design space determination.

7. Proving similarity with RLD and performing stability studies.

8. Deriving a control strategy.

2. Introduction

2.1 Introduction to Tablet [1] [2] [3] [4] [5]

Tablet can be defined as a compacted solid dosage form containing medicaments with or without excipients. As per Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without excipients. They differ in shape and greatly in size and weight, depending on quantity of actives and the required mode of administration. It is the most accepted dosage form and 70% of the total medicines are dispensed in the form of tablets. All the actives are available in the tablet form except those which are not suitable to formulate or administer in the tablet dosage form.

The advantages of the tablet dosage form are:

- They are single unit dosage form
- Offer the greatest capabilities of all oral dosage form for the greatest dose precision
- The least content variability
- Lower cost
- Lighter and compact
- Easy and cheap to package and strip
- Easy to swallow
- Different release profile can be achieved with the help of different polymers
- Taste masking is possible
- Suitable dosage form for large scale production
- Greatest chemical and microbial stability can be achieved
- Product identification can be carried out easily
- Require no additional steps when embossed and/or monogrammed punch face are employed.

Disadvantages of tablet dosage form are:

- Difficulty in swallowing for children, unconscious patients and geriatric patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate as a tablet that will still provide adequate drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.

Types of Tablets

(A) Tablets which are ingested orally are as under:

1. Compressed tablet
2. Multiple compressed tablet
3. Repeat action tablet
4. Delayed release tablet
5. Sugar coated tablet
6. Film coated tablet
7. Chewable tablet

(B) Tablets which are used in oral cavity are as under:

1.Buccal tablet

2.Sublingual tablet

3.Troches or lozenges

4.Dental cone

(C) Tablets administered by other route are as under:

1. Implantation tablet
2. Vaginal tablet

(D) Tablets used to prepare solution are as under:

1. Effervescent tablet
2. Dispensing tablet
3. Hypodermic tablet
4. Tablet triturates

Evaluation of Tablet

1. General Appearance:

- The common appearance of a tablet, its uniqueness is essential for the patient compliance and maintainenance of uniformity amongst the batches.
- The control of the characteristics like the measurement of size, shape, color, odor, taste etc. is required.

2. Size & Shape:

- This characteristic includes thickness which is a variable parameter.
- Tablet thickness is measured by digital vernier caliper.
- It should be restricted within a ± 5% variation of standard value.

3. Unique identification marking:

- These marking make use of some form of embossing, engraving or printing.

4. Organoleptic properties:

- Color distribution must be uniform.
- For visual color comparison compare the color of sample against standard color.

5. Hardness and Friability:

- Tablet requires a definite amount of strength and resistance to friability to resist mechanical shakes of usage in manufacture, packaging and shipping.
- Hardness generally measures the tablet crushing strength.

- Tablet hardness can be defined as the force required for breaking a tablet in a diametric compression. Generally used Hardness testers are:

    1. Monsanto Tester
    2. Strong-Cobb Tester
    3. Pfizer Tester
    4. Erweka Tester
    5. Schleuniger Tester

- Friability of a tablet can be determined in laboratory by Roche friabilator.
- This consists of a plastic chamber that revolves at 25 rpm, dropping the tablets from a distance of six inches in the friabilator, which is then operated for 100 revolutions. The tablets are reweighed.
- Compressed tablet that lose less than 0.5 to 1.0 % of the tablet weigh are considered as acceptable.

6. Drug Content and Release:

- Weight Variation test
- Content Uniformity Test
- Disintegration Test
- Dissolution Testing

Defects of Tablets

(1) Capping & Lamination:

- Complete or partial loss of top and bottom crowns of a tablet from the major body is called capping.
- The separation of a tablet into two or more distinct layers is called lamination.
- These problems occur immediately after compression, but may occur after several hours or days.

Causes:

- Air entrapment
- Deep concave punch
- Claw formation of Punch
- Wear ring formation in die wall
- Incorrect setting of the press
- Compression of too dry material

Remedy:

- By pre-compression
- Slowing tableting
- Reducing final compression force
- Using flat punch
- Using hygroscopic materials to maintain proper moisture level

(2) Picking & Sticking:

- Surface materials are removed from the tablets from a tablet by sticking to the punch is picking.
- Sticking refers to tablet materials adhering to the die wall. When sticking occurs, extra force is required to prevail over the friction between the tablets and die wall at some stage in ejection.

Cause:

Picking occurs when punch tips are engraving or embossing.

(3) Mottling:

It is an uneven distribution of colors on a tablet by light and dark areas on tablet surface.

Cause:

- Use of a drug whose color differs from tablet excipients.
- Use of a drug whose dehydration products are colored.

Remedy:

The use of colorant may solve the problem.

(4) Weight Variation:

Variation of tablet weight also causes variation of active which changes the bioavailability.

Cause

- **Granule size & size distribution:** Variations in the ratio of small to large granules and difference in granule size establishes how the void space between particles is filled. Since volume of die cavity remains same, different proportions of large and small particles may change the weight of fill in each die.

- **Poor Flow:** The die fill process is based on a continuous and uniform flow of granules via the hopper all the way through the feed frame. When the granules do not flow uniformly some dies are incompletely filled. With poor flow the addition of a glidant such as talcum or colloidal silica may be helpful. Depending on the geometry of the hopper, poor flow give rise to another troubles like bridging & rat holing.

(5) Arching or Bridging:

- Granules separate at the neck of the hopper and flow stops completely.
- Addition of glidant to prevent flow can overcome the problem.

(6) Rat Holling:

- In this case particles segregate near the wall of the hopper and at the center flow continues forming hole.
- In rat holling flow rate decreases which can be overcome by using glidant.

(7) Hardness Variation:

- Hardness depends on the weight of materials and space between upper and lower punch at the moment of compression.
- If the volume of materials and distance between the punches varies hardness also alters.

(8) Double Impression:

- This involves only punches that have monogram or engraving. If the monogram is present in upper punch, slight rotation of punch after pre-compression produce double impression.
- If monogram is present in lower punch then after compression is over, lower punch moves slightly downward to free the tablet and produces double impression.
- This problem can be overcome with the use of non-rotating cam track.

2.2 Introduction to Hypertension [6][7][8][9][10][11]

The blood circulates in the body through various blood vessels. With each heartbeat, some amount of freshly oxygenated blood is forced out of the left ventricle, into the aorta. The aorta is divided into major tree trunks. It is divided into smaller arteries, which in turn split into still smaller vessels known as arterioles, which take blood to the capillaries.

Capillaries are the small vessels that distribute blood, with its weight of oxygen and other nutrients, to each cell in the body. After the oxygen is consumed, the blood returns to the heart all the way through veins. A definite amount of force is required to keep blood moving all the way through this complex system of blood vessels. The extent of force that is exerted on the artery walls as blood flows through these walls is what known as blood pressure. To raise the blood pressure, the arterioles gets constructed or constrict to lower it, they open up or dilates.

Blood does not flow in a single stable stream, but, it moves all the way through the circulatory system that correlates with the heart beats. Heart is not contracting all the time, after each contraction, the heart muscle rests and gets set for the next beat. Blood pressure rises and falls with each beat. Thus, blood pressure is expressed in two numbers, such as 120 over 80. The higher number, which is called systolic pressure, represents the highest force that is exerted on the walls of the blood vessels at some stage in a heartbeat. The lower number, which is called as diastolic pressure.

Etiology of hypertension

In the most common cases, over 90 %, no exact cause for the high blood pressure is identified. In this case, the elevated blood pressure is known as primary hypertension. This type of elevated blood pressure may possibly be due to many factors like hormonal factors involving the managing of salt by the kidneys and/or to the extension of certain substances that cause restriction of blood vessels. These are possibly genetically determined, but specific environmental factors, such as a high-salt, low-potassium diet and chronic stress, may take part in some role. The causes for the same are as follows:

- Kidney disorders
- Renovascular hypertension
- Adrenal tumors
- Drugs
- Pheochromocytoma

Table 2.1: Classification of hypertension as per WHO

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal BP	Below 130	Below 85
High Normal BP	130-139	85-89
Mild hypertension	140-159	90-99
Moderate hypertension	160-179	100-109
Severe hypertension	180-209	110-119
Very severe hypertension	210 or higher	120 or higher

Treatment of Hypertension

A variety of effective medications to control high blood pressure are being developed since many years. Before advancements in the medications, treatment was limited to strict restriction of sodium, radical surgical processes, and drugs such as Phenobarbital that were not mostly effective. By that time the patients developed malignant or accelerated hypertension.

Classification of Antihypertensive Agents

1. **Diuretics**
   Thiazide: Hydrochlorthiazide, Chlorthalidone
   High ceiling: Furosemide
   K+ sparing: Spironolactone, Triamterene, Amiloride
2. **Centrally Acting Drugs**: Clonidine, Methyldopa
3. **Calcium Channel Blockers**: Verapamil, Diltiazem, Felodipine, Amlodipine
4. **Angiotensin Converting Enzyme (ACE) Inhibitors**: Captopril, Enalapril
5. **Angiotensin Receptor Blockers**: Losartan, Valsartan, Telmisartan
6. **β-adrenergic blockers**
   Non-selective: Propranolol
   Cardioselective: Metoprolol

These non-drug treatments include some lifestyle changes which are as under:

1. Reducing sodium intake
2. Maintaining a moderate alcohol intake
3. Losing excess weight
4. Increasing physical activity

2.3 Introduction to Quality by Design (Qbd) [12][13][14][15][16][17][18][19][20]

QbD is a scientific, systematic and holistic approach wherein product specifications, manufacturing procedure and critical parameters are taken into consideration in order to relieve the final approval and ongoing quality control of new medicine. FDA defines QbD as a systematic approach to improve those methods that starts with predefined objectives, and gives importance to product and process understanding, on the basis of scientific knowledge and risk management process.

QbD needs a proper understanding of influence of the product and process variables on the product quality. After its consideration by FDA in its c-GMP program, other two main guidances were made available as a part of ICH guidelines which are: **Q8**-Pharmaceutical Development and **Q9**-Quality Risk Management. The former explains the vision for the pharmaceutical development sector of the Common Technical Document (CTD); the later represents the approach to produce quality pharmaceutical products by means of current quality.

Table 2.2: Comparison between traditional approach and QbD approach

Aspects	Traditional Approach	QbD Approach
Product design	Screening of the best parameters	Target developed though wider use of prior knowledge, understanding of manufacturability
Pharmaceutical development	Empirical; typically univariate approach	Systematic; multivariate experiments, PAT tools used
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process control	In-process testing. Off line analysis	PAT tools utilized for feedback and feed forward controls
Product specification	Primary means of control; Mainly based on batch data at time of submission	Part of the overall quality control strategy; totally based on desired product performance
Control Strategy	By intermediate and end product testing	Risk based approach; reducing product variability; real time release
Life cycle management	Reactive to problems; post approval changes needed	Continuous improvement facilitated.

The characteristics of a successful QbD program are as under:

- Improvement in product design and process development
- Risk-based, science based systematic approach
- Considers Patient safety and product efficacy
- Business benefits
- Improved process understanding
- Improved process capability/robustness
- Multivariate – interactions are modeled
- Provides PAR, design space, or suitable equivalent
- Ensures a significant reduction in regulatory work

Key steps in QbD based product development are as under:

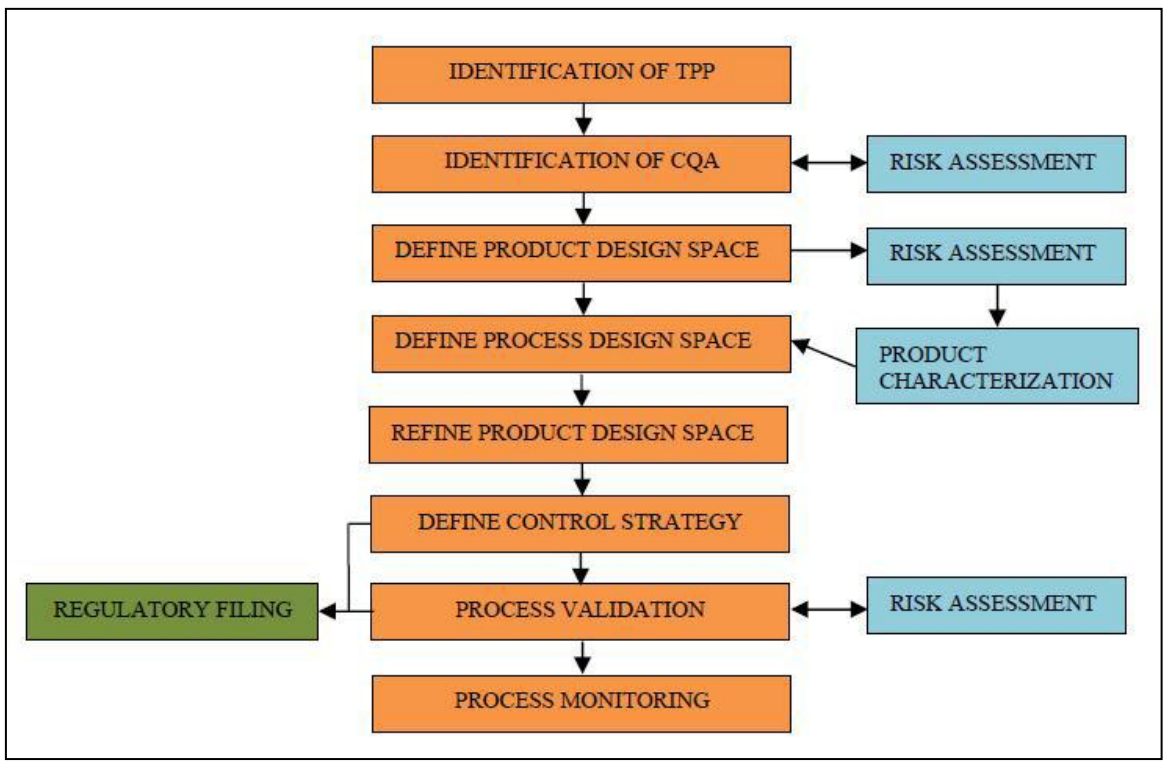


Figure 2.1: Flow chart of steps involved in QbD

1. Identifying Quality Target Product Profile (QTPP):

The TPP has been defined as a potential and dynamic summary of the quality uniqueness of a drug product that possibly will be achieved to make sure that the preferred quality, and therefore the safety and effectiveness, of a drug product is improved. For e.g. dosage form, route of administration, strength(s), release rate, pharmacokinetic characteristics appropriate to the drug product dosage form which is to be developed. The thought of TPP in this form and its purpose is novel in the QbD model.

2. Identifying CQAs:

After TPP has been identified, the succeeding step is to make out the appropriate CQAs. A CQA is defined as a physical, chemical, biological, or microbiological property that should be within an appropriate limit, to make sure that the desired product quality is achieved. Identification of CQAs is carried out through risk assessment. Knowledge of prior product with a precise product-quality attribute, is the way to make these risk assessments.

3. Design Product and Defining Product Design Space:

After CQAs for a product have been identified, the following step is to generate the product design and design space. These specifications are identified on the basis of several sources of information which are related to the attributes of safety and effectiveness of the product.

4. Process Design and Defining Process Design Space:

Process and product design and development cannot be divided since formulation cannot turn out to be a product restricted to a process. Design of a process is the primary stage of process development where a summary of commercial manufacturing process is recognized. This should consider all the factors that need to be measured to carry out any work. Critical process parameters are process inputs that include an important effect on critical quality attributes when they are used within normal process range.

5. Defining Control Strategy:

Control strategy is defined as a planned set of controls, derived from product and process understanding to ensure process performance and quality. The control strategy in the QbD model is recognized via risk evaluation that takes into account the criticality of the CQA and process ability. The control strategy consists of the following elements:

- In-process controls
- Lot-lot release testing
- Online monitoring
- Tests of parameters
- Stability testing

6. Regulatory Filings:

After the process design space is known and validated, the regulatory filing consists of the appropriate ranges for all key and critical operating parameters that describe the process design space over and above the additional restricted operating space described for drug products.

7. Process Monitoring, Life-Cycle Management and Continuous Improvement:

After approval, CQAs would be monitored to make sure that the process is performing in the range of the specific tolerable irregularity that was found as the root for the filed process design space. The main benefit of an expanded process design space would be an additional flexible approach by regulatory agencies.

2.5 Introduction to Excipients [21] [40] [41]

- **Nonproprietary Names**

BP	Lactose monohydrate
PhEur	Lactosum monohydricum
JP	Lactose
USP NF	Lactose monohydrate

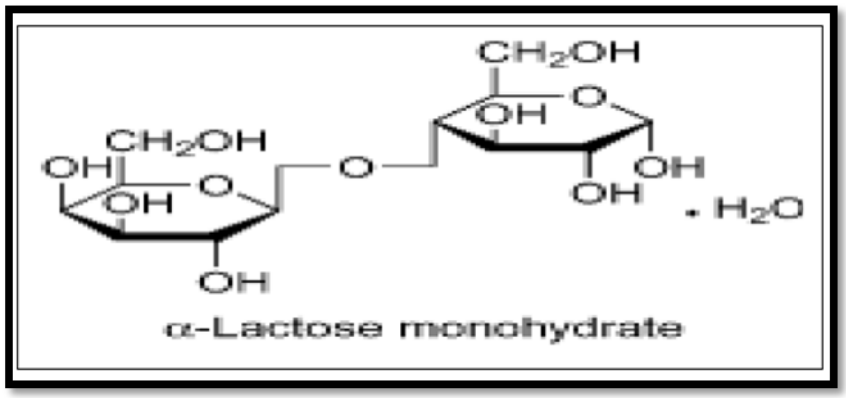
- **Chemical Name**

  O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate

- **Empirical Formula :** $C_{12}H_{22}O_{11}\cdot H_2O$

- **Molecular Weight :** 360.31

- **Structural Formula**



- **Functional Category**
  - Binding agent
  - Diluents for dry-powder inhalers
  - Tablet binder;
  - Tablet and capsule diluents

- **Description**

Chemical nature

- In the solid state, lactose appears as different isomeric forms, depending on the crystallization and drying conditions, which are α-lactose monohydrate, β-lactose anhydrous, and α-lactose-anhydrous.
- The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose-anhydrous, and stable α-lactose anhydrous.

Physical nature

- Lactose occurs as white to off-white crystalline particles or powder.
- Lactose is odorless and slightly sweet-tasting.

- **Typical Properties**

Density (true)	1.545 g/cc
Bulk Density	0.540 g/cc
Tapped Density	0.800 g/cc
Loss on drying	0.2% for Monohydrate
Melting point	201–202°C
Moisture content	5% w/w water of crystallization

Applications in Pharmaceutical Technology

- Lactose is used as diluents or filler in tablets and capsules.
- Different grades of lactose have their individual applications, for e.g. fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out.
- The grades which are generally used for direct compression are available as granulated/agglomerated α-lactose monohydrate.

- **Stability**

  Mold growth may occur under humid conditions.

  Lactose may develop a brown coloration on storage

- **Storage**

  It should be stored in a well-closed container in a cool and dry place.

2. Microcrystalline cellulose

- **Nonproprietary Names**

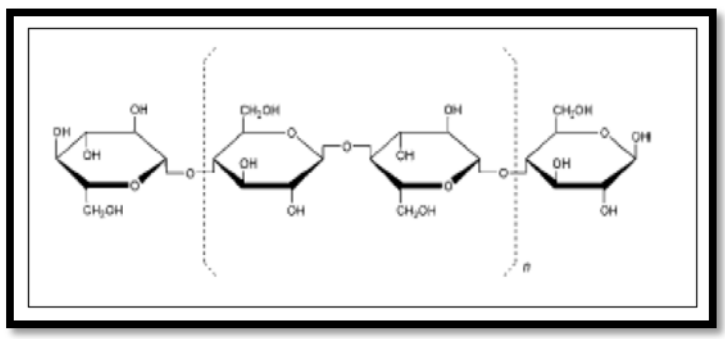
BP	Microcrystalline cellulose
PhEur	Cellulosum microcristallinum
JP	Microcrystalline cellulose
USP NF	Microcrystalline cellulose

- **Synonyms**

  Avicel PH, cellulose gel, Celphere, Ceolus

- **Empirical Formula :** $(C_6H_{10}O_5)_n$, where n=220

- **Structural Formula**



➢ **Functional Category**

- Adsorbent
- Suspending agent
- Tablet and capsule diluent
- Tablet disintegrants

➢ **Description**

- Microcrystalline cellulose is purified, partially depolymerized cellulose.
- It occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

➢ **Applications in Pharmaceutical Formulation or Technology**

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.

➢ **Typical Properties**

Density (true)	1.512–1.668 g/cm^3
Density (bulk)	0.337 g/cm^3
Density (tapped)	0.478 g/cm^3
Melting point	260–270 °C
Moisture content	less than 5% w/w

➢ **Incompatibilities**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

3. Magnesium stearate

- **Nonproprietary Names**

BP	Magnesium stearate
PhEur	Magnesii stearas
JP	Magnesium stearate
USP NF	Magnesium stearate

- **Synonyms**

  Magnesium octadecanoate, magnesium salt; stearic acid, magnesium salt.

- **Empirical Formula:** $C_{36}H_{70}MgO_4$

- **Molecular Weight:** 591.34

- **Structural Formula:** $[CH_3(CH_2)_{16}COO]_2Mg$

- **Functional Category :** Tablet and capsule lubricant

- **Applications in Pharmaceutical Technology**

- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

- **Description**

- Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.
- The powder is greasy to the touch and readily adheres to the skin.

- **Typical Properties**

Density (true)	1.092 g/cm^3
Density (bulk)	0.159 g/cm^3
Density (tapped)	0.286 g/cm^3
Flowability	Poorly flowing, cohesive powder
Melting point	117–150°C

- **Solubility:**

  Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

- **Incompatibilities**

  Incompatible with strong acids, alkalis, and iron salts.

4. Hydroxypropyl Cellulose

- **Nonproprietary Names**

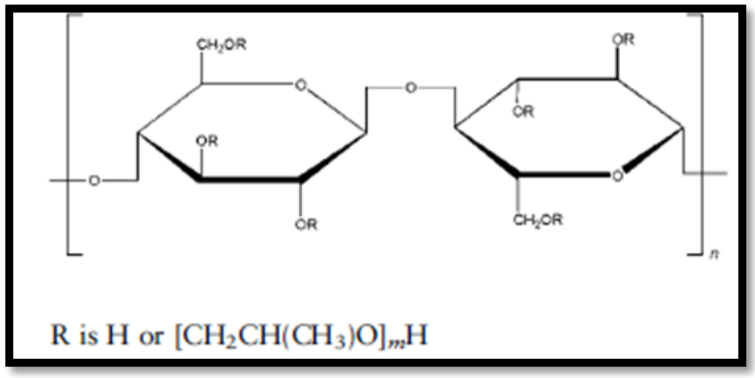
BP	Hydroxypropylcellulose
PhEur	Hydroxypropylcellulosum
JP	Hydroxypropylcellulose
USP NF	Hydroxypropyl cellulose

- **Synonyms**

Cellulose, hydroxypropyl ether; E463, hyprolose, Klucel

- **Molecular Weight:** 50 000–1 250 000

- **Structural Formula:**



➢ **Functional Category :**

- Coating agent
- Film-former
- Rate-controlling polymer for sustained release
- Stabilizing agent
- Suspending agent
- Tablet binder
- Viscosity-increasing agent

➢ **Applications in Pharmaceutical Technology**

It is widely used in oral and topical formulations.

Table 2.3: Uses of HPC

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

➢ **Description**

HPC is a white to slightly yellow-colored, odorless and tasteless powder.

- **Grades of Hydroxypropyl Cellulose**

Grades	Molecular weight
Klucel EF	80 000
Klucel LF	95 000
Klucel JF	140 000
Klucel GF	370 000
Klucel MF	850 000
Klucel HF	1 150 000

- **Typical properties**

Density (bulk)	0.5 g/cm3
Interfacial tension	12.5mN/m for a 0.1% w/v aqueous solution
Melting point	260–2758C.
Solubility	soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water

- **Incompatibilities**

- Incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben.

- **Stability**

It is stable, though it is hygroscopic after drying.

- **Storage**

It should be stored in a well closed container in a cool and dry place

5. Hydroxypropyl Cellulose, low substituted

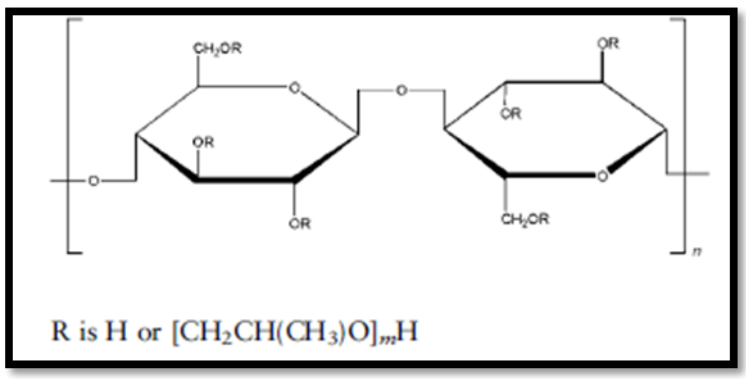
- **Nonproprietary Names**

BP	-
PhEur	-
JP	Low-substituted hydroxypropylcellulose
USP NF	Low-substituted hydroxypropyl cellulose

- **Synonyms**

  Hyprolose, low-substituted; L-HPC

- **Structural Formula:**



- **Functional Category**
  - Tablet and capsule disintegrant
  - Tablet binder

- **Applications in Pharmaceutical Technology**
  - L- HPC is mostly used in oral solid-dosage forms.
  - It is mainly used in tableting as a disintegrant, and as a binder in wet granulation. It can be used in the preparation of rapidly disintegrating tablets formed by direct compression method.

- L- HPC has been used to delay the release of drug from a tablet matrix.

Table 2.4: Applications of different grades of L-HPC

Grades	Application
LH 11	Anticappping agent and disintegrant for direct compression
LH 21	Binder and disintegrant for tablets by wet granulation
LH 31	In extrusion to produce granules
LH 22 & LH 32	It is used when higher binding strength is not required
LH 20 & LH 30	It is used when higher binding strength is required

➢ **Description**

- L-HPC occurs as a white to yellowish white powder or granules.
- It is odorless or has a slight, characteristic odor, and it is tasteless.

➢ **Stability and Storage Conditions**

- L-HPC is a stable, though hygroscopic, material.
- The powder should be stored in a wellclosed container.

6. Polyethylene glycol

➢ **Nonproprietary Names**

BP	Macrogols
PhEur	Macrogols
USP NF	Polyethylene glycol

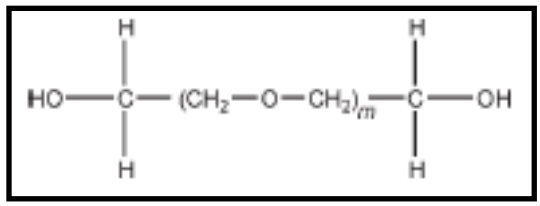
➢ **Synonyms**

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol

- **Empirical Formula:** HOCH2(CH2OCH2)mCH2OH where m represents the average number of oxyethylene groups.

- **Molecular Weight:** 570–613

- **Structural Formula**



- **Functional Category**

  - Antimicrobial preservative
  - Disinfectant
  - Plasticizer
  - Solvent
  - Stabilizer for vitamins
  - Water-miscible co-solvent

- **Applications in Pharmaceutical Formulation Technology**

- It has been widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations.
- It is a general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), and most alkaloids.
- As an antiseptic it is comparable to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.
- It is commonly used as a plasticizer in aqueous film-coating formulations.

- **Description**

  Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

- **Typical Properties**

Properties	**Data**
Boiling point	188°C
Density	1.038 g/cm^3
Melting point	-59°C
Solubility	Miscible with acetone, chloroform, ethanol (95%), glycerin, and water;

- **Stability and Storage Conditions**

- Polyethylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid.
- It is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

- **Incompatibilities**

All grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

3. Literature Survey

3.1 Literature Review on Dosage Form

1. ***S muira et al*** [10] The focus of this article was the understanding the safe and effective use of different Angiotensin Receptor Blockers (ARBs). It was reported that the effects of different ARBs were different from each other due to their different molecular structures The results reported in this article highlighted the different character of ARBs, and suggest that the higher degree of acceptability, slower dissociation, and higher affinity of one compared to another for AT1 receptors may help it to form a tight binding complex with this receptor. An improved understanding of the diverse molecular mechanisms for each ARB could be useful for the treatment of patients.

2. ***Keijiro Saku et al*** [9] The focus of this review was to give the information about the link between the AT-1 receptors and the ARBs. It also gave the information about the difference in the therapeutic effect of all the drugs in the class of ARBs. On the other hand, it was controversial whether ARBs had molecular effects in a clinical setting. Although the presence of molecular effects for each ARB on the basis of experimental studies may not directly influence the clinical outcome. Hence, this review focused on the class effects vs. molecular effects of ARBs.

3. ***M.A. Odeniyi et al*** [22] A research study was made on the compressibility and flow characteristics of Metronidazole in binary mixtures with Lactose and Microcrystalline cellulose powders as diluents. Binary mixtures of various proportions of Metronidazole with Lactose powder and microcrystalline cellulose were prepared. The bulk and tapped densities, angle of repose, angle of internal flow, and compressibility index of the individual and powder mixtures were determined using appropriate parameters. The results obtained showed that the packing and cohesive properties of the binary mixtures depended on the nature of the diluent, particle shape and size, particle size distribution, and the concentration of the diluent. The results from the factorial experimental design showed that changing the diluent from low to high concentration in both mixtures served to increase the maximum

volume reduction parameter, while no significant ($p > 0.05$) effect was observed when the diluent was changed from Lactose to Microcrystalline cellulose. However, changes in the nature and concentration of diluents caused an increase in the angle of internal flow. The results obtained would be useful in the handling and industrial processing of these powders and in the production of powders, tablets, capsules and other drug delivery systems with desirable and predictable flow properties.

4. Mayur et al [23] The focus of this research work was to compare the effect of the wet granulation and direct compression method for the preparation of the immediate release tablets of antihypertensive agent. The formulation was checked for all pharmacopoeial specifications of IR tablets and was found to be competent with them. The results of the optimized formula were found to be comparable with that of the marketed formulation.

5. D.Oulhana et al [24] The focus of this investigation was to check the effect of impeller speed on granule properties in high shear granulation. The results of this investigation on wet granulation of fine powders have shown greater effect on granule growth and their final properties like porosity, friability and binder content. It was found that the higher the impeller speed lower is the porosity and friability of the granules and narrower is the particle size distribution; increasing shear did not yield in homogeneous granules. Granule properties depend on their size, at any impeller speed and for low shear granulation friability was not linked with the binder ratio.

3.2 Literature Review on Quality by Design

1. *Gupta Anuj et al* [25] The focus of this review was to discuss the concept of pharmaceutical Quality by Design (QbD) and describe its usefulness to achieve pharmaceutical quality. QbD is an important part of the modern approach to pharmaceutical quality. The elements of quality by design were examined and explained as which consisted critical quality attribute, critical process parameter, critical material attribute, and control strategy. The use of QbD was contrasted with the evaluation of product quality by testing alone. It was concluded that by using

QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables.

2. *Jun Haung et al* [26] The focus of this investigation was to find out the root-cause of tablet dissolution shift (slow-down) upon stability by using experimental design, carrying out optimization and multivariate techniques. The research was carried out as there was a slow down observed in the dissolution during a 4 week accelerated stability study under 51°C/75% RH storage condition. An experimental design was carried out to see the impact of the interactions and effects of the design factors on critical quality attribute (CQA) of dissolution on stability. The design space was examined by design of experiment (DoE) and multivariate analysis to ensure desired dissolution profile and minimum dissolution shift on stability. Multivariate techniques like multi-way principal component analysis (MPCA) of all the dissolution profiles on stability were performed to get knowledge about the batch relationships and to evaluate the impact of design factors on dissolution.

3. *Sherif Badawy et al* [27] The focus of this investigation was to find out the effect of four process parameters using the design of experiment approach. All the batches were characterized for particle size distribution, flow, compaction, density and dissolution rate. The mechanisms of all the process parameters on granule properties were proposed. The impact of water amount, water addition rate, impeller speed and wet massing time was checked on the granule properties. Water amount showed significant effect on granule size and density. The impact of impeller speed was dependent on the granule mechanical properties and efficiency of liquid distribution in the granulator. Blend density was found to increase rapidly during wet massing. Liquid addition rate was the least consequential factor and showed minimum impact on granule density and growth.

3.3 Literature Review on Patents

1. US patent 1: It claims a dosage form comprising of an ester of the drug DM01 having particle size of $d_{0.9}$< 140µm and stearic acid, characterized in such a way that

the amount of acidic impurity does not increase >2.0% on storage at 60^0 for 1 week. A composition with DM01 drug, characterized in that when exposed to 75% RH at 40^0 in open dish for 1 month the total amount of related substances does not increase more than 1%.

2. US patent 2: It claims a solid dosage form of the drug DM01 having improved stability with low impurities and good flowability. It also claims lubricant or lubricants and coating agents of tablet core in that the lubricant is from the group of calcium stearate, zinc and sodium stearyl fumarate or their mixture.

3. PCT application 2: It claims a solid oral dosage form comprising of drug DM01 and polyethylene glycol (PEG) with average weight of 5000-10,000, as a stabilizer. The proposed method of preparation is by wet granulation where PEG stabilizes the drug.

4. Materials and Methods

4.1 List of Equipments and Materials

Table 4.1: List of materials

Sr. No	Excipients	Grade	Manufacturer	Function
1.	Lactose Monohydrate	USP-NF/PhEur	DMV Fonterra	Binder
2.	Hydroxypropyl cellulose (Klucel EXF)	USP-NF/PhEur	Aqualon Division	Binder
3.	Low substituted Hydroxypropyl cellulose (LH-21)	USP-NF	Shin Etsu Chemicals	Disintegrating Agent
4.	Microcrystalline cellulose(Avicel PH 101)	USP-NF/PhEur	JRS Pharma	Intra granular diluent
5.	Microcrystalline cellulose(Avicel PH 102)	USP-NF/PhEur	JRS Pharma	Extra Granular Diluent
5.	Magnesium stearate	USP-NF/PhEur	Merck KGAA	Lubricating Agent
6.	Hypromellose 6 cps	USP-NF/PhEur	Dow Chemicals	Film Former
7.	Titanium Dioxide	USP-NF/PhEur	Kronos Pharmaceutical Ltd.	Opacifier
8.	Purified Talc	USP/PhEur	Imerys Talc	Anticaking Agent
9.	Ferric oxide yellow	USNF	Rockwood Italia	Coloring agent

Table 4.2: List of equipments

Equipments	Company
Double cone blender	Elicon® pharma, Mumbai, India
Electronic weighing balance	Mettler Toledo®, Mumbai, India
Single rotary tablet compression machine (16 station)	Chamunda® Machinery, Ahmedabad, India
Rapid mixture granulator (RMG)	Saral® engineering, Vapi, Gujarat
Moisture analyzer	Mettler® Toledo, Mumbai, India
Fluidized bed dryer	GEA® pharma, Vadodra, Gujarat

Friabilator	Electrolab®, Mumbai, India

4.2 Methodology *(28) (29) (30) (32)*

The experimental work was carried out using the concept of Quality of Design, which includes the elements like QTPP, CQAs, CPPs, design space, risk assessment, control strategy. The tool of Design of Experiment helps to generate a proper design space for the product development.

4.2.1 Pre-formulation Study

Pre-formulation may be defined as a critical part of research and development procedure which includes the characterization of the physical, chemical and mechanical properties of a drug substance with the objective of developing stable, safe and effective dosage form.

The pre-formulation study was carried out for the preparation of immediate release tablets of DM01 using the concept of QbD which includes the following analysis of the API.

Table 4.3: List of properties

Section	Properties of DM01	Properties Studied
4.2.1.1	Pharmacodynamic properties	Mechanism of Action, Dosage and Administration, Indications
4.2.1.2	Pharmacokinetic Properties	Absorption, Distribution, Metabolism, Excretion
4.2.1.3	Physical Properties	Micromeritic Properties, Solubility, Hygroscopicity, Polymorphism
4.2.1.4	Chemical Properties	pKa, chemical analysis, forced degradation study
4.2.1.5	Biological Properties	Partition coefficient, BCS classification
4.2.1.6	Compatibility	Drug-Excipient Compatibility Study

4.2.1.1 Pharmacodynamic Properties

The pharmacodynamic properties of DM01 were noted on the basis of literature analysis. It includes the properties like mechanism of action, dosage and administration and indications. These properties are shown in section 4.3.1.1.

4.2.1.2 Pharmacokinetic Properties

The pharmacodynamic properties of DM01 were noted on the basis of literature analysis. It includes absorption, distribution, metabolism and excretion. These properties are shown in section 4.3.1.2

4.2.1.3 Physical Properties

4.2.1.3A Description

The powder sample of DM01 was observed physically. The observations are given in section 4.3.1.3A

4.2.1.3B Micromeritic Properties

1. **Bulk Density and Tapped Density**[30]

   Approximately, 10 g powder was weighed and filled up in 100 ml measuring cylinder. The volume occupied by the powder was noted as V_0, without disturbing the cylinder. The cylinder was set in the tapped density measurement apparatus. After 10 taps, volume was noted as V_c. Again after 500 taps volume was noted as V_b. The difference between V_b and V_c must be less than or equal to 2 ml. V_c is the tapped volume. Bulk density (BD) and tapped density (TD) were then calculated by using the following formula. It can be measured in g/ml.

$$B.D = \frac{Weight}{Bulk\ Volume} \qquad T.D = \frac{Weight}{Tapped\ Volume}$$

2. Compressibility

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values greater than 21% have been found to exhibit poor flow properties.

$$Compressibility\ Index = \frac{T\ D - B\ D}{TD} * 100 \qquad Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

Where, *TD* = Tapped density

BD= Bulk density

Table 4.4: Criteria for powder flow properties

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.1-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	**Very poor**	**1.46-1.59**
>38	Very, very poor	>1.60

4.2.1.3C Particle Size Analysis

Various physical and chemical properties of drug substance are affected by their particle size distribution and shape. The effect is not only on the physical properties of solid but also on their biopharmaceutical behavior. Particle size was determined by Dry method using Malvern Mastersizer Equipment.

4.2.1.3D Aqueous solubility as a function of pH

1 gm of drug was added in 250 ml of solvent (i.e. purified water, acetate as well as phosphate buffers of different pH with/without SLS) and kept overnight (for 24 hrs). Dispersions were filtered using whattman filter paper and the filtrate samples were analyzed using UV-visible spectrometer. The solubility of drug was calculated from the amount of drug solubilized. The solubility of DM01 in different pH ranges of the

gastrointestinal tract was determined to aid in selecting suitable dissolution media for development purpose and to ensure that 'sink conditions' are maintained therein.

4.2.1.3E Hygroscopicity studies

Hygroscopicity study was performed for DM01 to get an idea about susceptibility of drug to storage condition moisture and its effect. DM01 was placed in two open petridish. One of the plates was kept in 30^{o}C/75% RH chamber whereas the other was placed in 25^{o}C/60% RH chamber. Control samples in sealed glass vials were also kept individually in each chamber. Percent water was analyzed at specific time intervals, till equilibrium was achieved.

4.2.1.4 Chemical Properties

4.2.1.4A Chemical Analysis of DM01

1. **Assay and Related Substances**

   In-house method was developed by ADL(analytical development laboratory)to perform the assay of DM01and to calculate the related substance present in DM01 by analytical development laboratory.

2. **Forced Degradation Data of DM01**

   Stress testing (forced degradation) was carried out on DM01 to evaluate its impurity profile and degradation pathway. The testing included the effect of temperatures higher than that used for accelerated testing, oxidation, acid and basic conditions, and photolysis on the drug substance. The stressed samples were compared to the unstressed sample (control). Stress conditions and results are listed in the table below. The objective of this stress study was to further understand the possible degradation pathway of the drug substance related to the specified impurities. In addition, the results from some of the stress conditions may also serve as a reference for formulation design/optimization and preventing the impurities generated during any of the storage conditions, and processing conditions of drug product manufacturing.

4.2.1.5 Biological Property

1. **Partition Coefficient(Log P)**

   The method to find partition coefficient value of DM01 was not performed, but on the basis of literature survey its value is mentioned in section 4.3.1.5 as a part of a biologic property of DM01.

2. **Bio-pharmaceutics Classification**

   Experimental data from literature supports the categorization of DM01 as a highly permeable drug substance. The method to prove the high permeability of DM01 was not performed. But the nature of low solubility was proved as per the method described in section 4.2.1.3D**.**

4.2.1.5 Drug-Excipient Compatibility Study

Drug and excipient compatibility study is an essential part of pre-formulation studies in which active ingredients are mixed with the excipients by physical mixing in different ratios and exposed to various stress conditions like:

- At 50°C (moist and dry): accelerated stability conditions of heat.
- At 25°C / 60 %RH: accelerated stability conditions of humidity
- At 40°C / 75 %RH: accelerated stability conditions of heat and humidity

Excipients compatibility study was performed keeping the mixture of the drug substance with different excipients at accelerated condition of 40°C/ 75 % RH and 50°C in glass vials. The samples were analyzed for any physical and chemical change after incubation for one month.

4.2.2 Evaluation of Tablets

The formulated tablets were subjected to following evaluation parameters:

4.2.2.1 Weight variation

Twenty tablets were weighed individually and the average weight was determined. The percent deviation was calculated and checked for weight variation. The Pharmacopoeial standards for weight variation of a tablet as shown in following table:

Table 4.5: Criteria for weight variation test

Average weight of tablet	% deviation
130 mg or less	10
More than 130 mg but less than 324 mg	7.5
324 mg or more	5

4.2.2.2 Thickness measurement

The thickness of prepared tablets was measured using a digital vernier caliper. Five tablets from each batch were utilized for this test.

4.2.2.3 Tablet Hardness

Tablet hardness is defined as the force necessary for breaking a tablet in a diametric compression test. It is measured in kilogram (kg), Newton (N), Pound (lb), kg/cm^2, kilopond (kp). Tablets require a certain amount of hardness or strength to withstand mechanical shocks of manufacturing, packaging, and shipping. Hardness of 5 tablets from each batch was measured using Monsanto hardness tester.

4.2.2.3 Friability test

Friability test was performed to evaluate the effect of friction and shock, which could frequently cause tablet to chip, cap or break. Friability of the tablets was determined using Electrolab® friabilator .This device subjected the tablets to collective effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropped the tablets from the height of 6 inches in each revolution. Tablets were weighed and placed in the

friabilator and were subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed.

The friability (*f*) was calculated using following formula:

$$f = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

4.2.2.4 In-vitro dissolution studies

The Development of a dissolution method that can act as the best available predictor of equivalent pharmacokinetics to the RLD was pursued to allow assessment of DM01 tablets manufactured during development. DM01 is a BCS Class II compound displaying pH dependent solubility across the physiological pH range and the minimum solubility observed at pH 4.5 i.e. 0.002mg/ml . So the dissolution had been performed in all three media mentioned below.

1) 0.1 N HCl
2) Acetate buffer pH 4.5
3) 0.05M Phosphate buffer, pH 6.8 (OGD Recommended Media)

The in-house method to perform the in-vitro dissolution studies was carried out by analytical development laboratory as follows.

Analytical procedure for dissolution

Preparation of dissolution medium: 6.8 g of potassium dihydrogen orthophosphate was dissolved in 950ml of water and adjusted for pH 6.8 with dilute sodium hydroxide.Final volume was made up to 1000ml with water.

Chromatographic parameters are as follows:

Column	: Peerless basic C18 (50*4.6 mm),5µ
Flow rate	: 1.5ml/min
Injection volume	: 50µl
Injector Temperature	: 10^0C
Column temperature	: 25^0C
Retention time	: About 1.5 min for DM01 peak
Run time	: 3 min

Buffer preparation: 1.36 g of potassium dihydrogen orthophosphate was dissolved in 950ml of water and adjusted for pH 3.00 with orthophosphoric acid(88%).Volume was made up to 1000ml with water. Solution was filtered through 0.45µ nylon filter.

Mobile Phase: A mixture of 550ml volume of buffer and 450 ml volume of acetonitrile was prepared.

Standard Preparation: Accurately weighed quantity of about 27.5 mg of DM01 working standard was transferred into 200ml volumetric flask.5ml methanol was added to dissolve and diluted to volume with dissolution media.2ml of the resulting solution was diluted up to 50 ml with dissolution media and mixed well.

Sample preparation:

1) Bowls are filled with required quantity of dissolution medium.
2) 6 tablets were dropped in 6 separate bowls and care was taken to exclude air bubbles from the surface of tablet. Apparatus was started immediately.
3) Samples were withdrawn at the given interval.
4) Filtered through nylon filter 0.45µ.
5) 2.5 ml of filtered sample was diluted with 20ml of dissolution media and mixed well.

Calculation:

%=Au/As*W1/200*2/50*900/40*P/100*100

Where,

Au : Peak area due to drug obtained with sample preparation.
As : Mean peak area due to drug obtained with standard preparation.
W1 : Weight of drug working standard taken in mg.
P : Potency of drug working standard in % on as is basis.

4.2.2.5 Analytical procedure for Assay

The in-house method to perform the assay of tablets was carried out by analytical development laboratory as under.

Chromatographic parameters are as follows:

Column	: Peerless basic C18 (100*4.6 mm), 5µ
Flow rate	: 1.5ml/min
Injection volume	: 25µl
Injector Temperature	: 4^0C
Column temperature	: 25^0C
Retention time	: About 3.0 min for DM01 peak
Run time	: 5 min

Buffer preparation: 1.36 g of potassium dihydrogen orthophosphate was dissolved in 950ml of water and adjusted for pH 3.00 with orthophosphoric acid (88%).Volume was made up to 1000ml with water. Solution was filtered through 0.45µ nylon filter.

Mobile Phase: A mixture of 550ml volume of buffer and 450 ml volume of acetonitrile was prepared.

Preparation of Diluent-1: A mixture containing 200 ml of water + 0.2ml orthophosphoric acid + 100 ml methanol + 700 ml of acetonitrile was prepared.

Preparation of Diluent-2: A mixture of 500ml of water + 500ml of methanol was prepared.

Standard preparation: Accurately weighed quantity of about 20 mg of drug working standard is transferred into 100ml volumetric flask. 50ml of diluent-1 was added while dissolving the drug and the volume was made up by diluent-1.2ml of the resulting solution was dissolved in 200ml of diluent-2 and mixed well. Solution was filtered with 0.45u nylon filter.

Assay preparation:

1) 5 whole tablets were transferred into 200ml volumetric flask.
2) 10ml of water and 150 ml of diluent-1 were added to volumetric flask and sonicated for 30min.
   (a) Volume was made up by diluent-1.
   (b) 2ml of resulting solution was diluted to 200ml by diluent-2 and mixed well.
   (c) Solution was filtered through 0.45µ nylon filter.

Average weight: 20 tablets were weighed accurately and their weight noted down. Gross weight of 20 tablets was divided by 20 to obtain the average weight of tablet.

Calculation:

%= Au/As*W1/100*5/100*200/W2*200/2*W3/L.C*P/100*100

Where,

Au : mean peak area due to drug obtained with assay preparation.

As : mean peak area due to drug obtained with standard preparation.

W1 : weight of drug working standard taken in mg.

W2 : weight of sample in taken in mg.

W3 : average weight of tablet in mg

L.C : label claim of drug in mg/tablet

P : potency of drug working standard in %

4.2.3 Characterization of Reference Product

The characterization of the reference tablets was performed for its physical properties and chemical properties including in-vitro dissolution studies. The physical properties which included the tablet evaluation parameters and dissolution study were characterized using the procedure mentioned in section 4.2.2.

4.2.4 Identification of Quality Target Product Profile (QTPP) [35]

Based upon the above clinical and pharmacokinetic characteristics of the tablet as per the product label, and in-vitro drug release and physicochemical characteristics as shown in section 4.4.1 and 4.4.2, and on the basis of prior knowledge, QTPP were defined to conduct the development of tablets that is therapeutically equivalent to the RLD.

4.2.5 Identification of Critical Quality Attributes (CQAs)

Based upon the product and process understanding, prior knowledge and experience, the CQAs were identified. The critical and non-critical attributes for the DM01 Tablet 40 mg is defined in **table.**

4.2.6 Risk Assessment of Drug Substance Attributes on Drug Product CQAs

The risk assessment of the drug substance attributes was carried out on the basis of prior knowledge and experience. The risk assessment is shown in **table.** The risk assessment was updated for revising the effect of each attribute on CQAs. The updated risk assessment is shown in **table** on the basis of prior knowledge and experience, with justifications. The risk assessment categorization and risk ranking was carried out on the following basis.

Risk ranking and Filtering:

Severity

Level	Score	Explanation
Minor	1	No impact
Major	2	Generation of impact will have moderate effect
Critical	3	Known impact on product quality as per specification

Risk Matrix

Probability / Severity	1	2	3
1	L	L	M
2	L	M	H
3	M	H	H

L=low, M=medium and H=high

Risk Score

Criticality	Score	Definition
Low	1-2	Broadly acceptable risk. No further investigation needed.
Medium	3-4	Risk is accepted. Further investigation may be needed in order to reduce the risk.
High	5 or above	Risk unacceptable. Further investigation required to reduce the risk.

4.2.7 Formulation Development

4.2.7.1 Risk Assessment of the Formulation Variables

The initial risk assessment of the formulation variables was carried out on the basis of prior knowledge and experience. The results are shown in **table**.

4.2.7.2 Risk Assessment of the Unit Operations

The risk assessment of the unit operations was carried out on the basis of prior knowledge and experience. The results are shown in **table**. The risk ranking was carried out as per the method described in section 4.2.6.

4.2.7.2 Formulation Strategy

The development work was initiated using excipients enlisted in reference product and literature for DM01 Tablets 40 mg. Initial formulation strategy for DM01 tablets 40 mg was tabulated below.

Table 4.6: Formula for DM01 Tablet 40 mg

Sr. No	Ingredient	40 mg
1.	DM01	40.0 mg
2.	Excipients	380.0 mg
Tablet weight		420.0 mg

Direct compression and wet granulation were the two strategies used to formulate as they are the most frequently employed methods for preparing immediate release tablet. Direct compression was firstly employed as it contains fewer processing steps. Later the strategy was dropped; justification for the same is given after the results of the direct compression batches in section

The wet granulation method was selected as an alternative of direct compression expecting a better result than the previous method. The use of wet granulation with an aqueous method was excluded due to potential degradation of drug substance by water hydrolysis based on the forced degradation data of drug substances as shown in **table.** Isopropyl alcohol (IPA) was selected as a granulating solvent which is classified as class 3 solvent

having low toxic potential (As per ICH Q3C). For wet granulation by rapid mixer granulator, the drug substance and excipients were subjected to mixing under high shear provided by impeller to achieve the uniform mixing of API.

Prototype formulation was developed based on the prior knowledge of drug product and based on the aforesaid formulation criteria.

4.2.7.2A Tablets prepared by Direct Compression

The formula for the batches of tablets prepared by direct compression is as given in **table**

1) Dispensing of the required ingredients in their respective quantities was done, followed by that, DM01 (drug), Lactose monohydrate, Hydroxyl propyl cellulose, Low substituted Hydroxypropyl cellulose (LH-21) and Microcrystalline cellulose were co sifted through sieve #30

2) Blending of dry mix for 10 min in double cone blender (0.5 L) at 24rpm.

3) Lubricant was shifted from sieve#60 and mixed with previous blend and blended in same blender for 5 mins at 20rpm.

4) Lubricated blend was compressed.

The results are as shown in section 4.4.5.3A.

4.2.7.2B Tablets prepared by Wet Granulation

Table 4.7: Formula for Tablets prepared by Direct Compression Manufacturing Process

Sr. No	Batch No.	4001	4002	4003	4004	4005
	Batch Size	2000 tablets				
	Ingredients	Qty/Tab (mg)				
Dry Mixing						
1.	Drug	40.00 (50µm)	40.00 (9µm)	40.00 (9µm)	40.00 (9µm)	40.00 (9µm)
2.	Microcellac 100	286.4	286.4	287.9	326.4	276.4
3.	HPC(KLUCEL EXF)	10.0	10.0	10.0	10.0	20.0
4.	L-HPC	80.0	80.0	80.0	40.0	80.0
Lubrication						
5.	Magnesium stearate	3.6	3.6	2.1	3.6	3.6
Theoretical weight of Tablet		**420.0**	**420.0**	**420.0**	**420.0**	**420.0**

Table 4.8: Unit Composition of DM01 Tablets 40 mg- GR5001

Sr. No	Batch No	GR5001
	Batch Size	**2000 Tablets**
	Ingredients	**Qty/Tablet (mg)**
Dry Mixing		
1.	DM01	40.00
2.	Lactose monohydrate	247.92
3.	Hydroxypropyl cellulose (Klucel EXF)	15.00
4.	Low substituted Hydroxypropyl cellulose (LH-21)	20.00
5.	Microcrystalline cellulose (Avicel PH 101)	35.00
Granulation		
5.	Isopropyl alcohol	Q.S.
Lubrication		
6.	Microcrystalline cellulose (Avicel pH 102)	40.00
7.	Low substituted Hydroxypropyl cellulose (LH-21)	20.00
8.	Magnesium stearate	2.08
	Theoretical weight of Core tablet	**420.00**

Manufacturing Procedure

(a) DM01, Lactose monohydrate, Hydroxyl propyl cellulose, Low substituted Hydroxypropyl cellulose (LH-21) and Microcrystalline cellulose were co sifted through sieve #30 and dry mixed in RMG for 10 min at slow Impeller speed.

(b) The resulting blend of step 1 was granulated by addition of Isopropyl alcohol (slow Impeller speed) followed by kneading:

	Impeller Speed	Chopper Speed	Time
Kneading	Fast	Off	30 sec
Kneading#	Slow	Off	30 sec

#: further kneading to be provided if required.

(c) Wet granules of step 2 were dried in rapid dryer at about temperature 45±10^{o}C till LOD achieved below 2.0%w/w.

(d) Dried granules were passed through sieve #30. The granules retained on 30# were collected and were milled through multimill equipped with 1.5 mm s.s screen (Speed: Medium, Knife: forward). The milled granules were sifted through 30#

sieve. Retained granules were milled through 0.5 mm screen in multimill (Speed: Fast, Knife Forward). Milled and sifted granules were collected in a polybag.

(e) Extragranular Microcrystalline cellulose and Low substituted Hydroxypropyl cellulose (LH-21) were co sifted through 30#.

(f) The material of step 5 and granules of step 4 were mixed in a blender for 10 mins at 24 RPM.

(g) Magnesium stearate was sifted through 60#. Sifted Magnesium stearate was added to blend of step 6 and further mixed for 5 min at 24 RPM.

(h) Lubricated blend of step 7 was compressed into tablets.

The results are as shown in section 4.4.5.3B.

The core tablets were subjected to film coating using non aqueous solvent system. The coating composition is tabulated as follows.

Table 4.9: Coating Composition of DM01 Tablets 40 mg

Sr. No	Ingredients	Qty/Tablet (mg)
	Strength	**40 mg**
	Batch No.	**GR5001**
	Batch Size	**2000 Tablets**
Coating		
1.	Uncoated Tablets	420.00
2.	HPMC 6 cps	6.20
3.	Talc	2.10
4.	Titanium Dioxide	2.10
5.	Dichloromethane	q.s.
6.	Isopropyl alcohol	q.s.
Theoretical weight of Coated tablet		**430.40**

Preparation of the film coating solution:

(a) Disperse HPMC 6 CPS in approximately half quantity of Isopropyl alcohol under continuous stirring for 10 min.

(b) Disperse Purified Talc, and Titanium dioxide and ferric oxide yellow in remaining qty of Isopropyl alcohol under continuous stirring. Pass this dispersion through colloid mill for 10 min.

(c) Add Methylene chloride to the dispersion of Step 1 under continuous stirring for 15 minutes.

(d) Add dispersion of step 2 to the solution of Step 3 under continuous stirring for 10 minutes.

(e) Filter the dispersion through 100# Sieve.

The coated tablets were evaluated for the in vitro drug release using phosphate buffer pH 6.8 as a release media. The drug release of DM01 tablets 40 mg was compared with Reference product and results are as given in **table.**

Batch GR5002 was taken to check the reproducibility of batch GR5001.

The evaluation of GR5002 is shown in section 4.4.5.3B.

4.2.7.2 Formulation Optimization

Formulation development was further focused on evaluation of the high risk formulation variables as identified in the initial risk assessment presented in table . The identified formulation variables was systematically evaluated and studied through statistical tools as part of quality by design approach.

Experimental Design:

Statistical approach in formulation development is the most preferred way to evaluate and understand the factors and their levels on the selected responses. In this case, it would be the attributes of the finished dosage form, i.e., tablets. The most commonly used and recommended one is "Design of Experiments" methodology. In the further paragraphs, this is abbreviated as DoE. To begin with DOE in the development of DM01 tablets, the different broad stages are briefly discussed in the below paragraphs.

In the first stage of DoE, referred as screening DoE, formulation variables that might impact the finished product attributes need to be studied and the outcome will be classification of potential/critical and non critical factors/variables. An DM01 tablet is an immediate release dosage form and is produced with conventional techniques known to formulation scientists. Additionally, based on the literature support and also based on reference product characteristics, product development was initiated. The outcome of preliminary and prototype formulation trials have given sufficient knowledge and based on which critical formulation variables were identified. Hence, at this stage of development, all the variables that have potential impact on the drug product were clearly visible and screening design approach has no purpose in the current stage of product development.

The second stage of DoE in the product development is referred as characterization DoE which is the most desirable approach was utilized and modulated appropriately for the drug product under development. In the case of DM01 tablets, this was implemented with an objective of understanding the criticality and intensity of identified factors on the selected response (CQA - Dissolution). This phase of experimentation would also provide enormous data that will help in finalizing the range of formulation variables in achieving drug product QTPP. Also the objective of this phase of experimentation is to establish the

interaction of factors, accuracy of prediction of the response within the identified design space.

Response surface methodology (RSM) is one of the popular methods in design of experiments, which involves the use of different types of experimental designs to generate polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimal ranges. Box-behnken design is part of RSM designs. The Box-behnken design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation variables on dissolution and disintegration which is one of the critical quality attribute of drug product. In this work, the Box-behnken design was used to obtain a design of space which determined the acceptable ranges of different formulation variables for achieving the desired product quality.

A Box-behnken with five center points was used to study the impact of the three formulation factors[Binder Concentration (% w/w),Disintegrant Concentration (Extra Granular),Kneading Time(sec) (% w/w)] on the response variables listed in table below.

The binder used is Klucel EXF and the level investigated ranged from 2.4 % to 4.8%. These levels are within the recommended range in the Handbook of Pharmaceutical Excipients. The Disintegrant was used is L-HPC and added both intra granular and extra granular. The intra granular level of disintegrant was fixed as per the prior knowledge of the product development. The extra granular disintegrant levels investigated ranged from 2.8% to 6.8%.

The drug load in the DM01 tablet formulation was fixed at 9.52% based on the RLD label, strength and tablet weight. The extra-granular magnesium stearate level was fixed at 1% which is agreeing with the recommendations published in the handbook of pharmaceutical excipients. A constant tablet weight of 420.0 mg was used with the filler amount adjusted to achieve the target weight. Procedure was kept same as mentioned in batch GR5001.

The design trial chart, design batches and their interpretation are shown in section 4.4.5.4.

4.2.7.3 Manufacturing Process Optimization

As a part of manufacturing process development initial risk assessment of the manufacturing process variables for different unit operation (compression and lubrication) was carried out on the optimized formulation of DM01 tablet 40 mg on the basis of prior knowledge and literature. The results are mentioned in section 4.4.5.5.

4.2.7.3 Stability Study [37]

Stability study for the tablets of optimized batch was carried out at two conditions (25°C/60% and 40°C/75%) for 2 months. The results are mentioned in section 4.4.5.6.

4.3 Control Strategy

The control strategy was given for raw material attributes; compression, blending and lubrication on the basis of results obtained by formulation & process optimization and overall process understanding.

4.4 Result & Discussion

4.4.1 Pre-formulation Study

4.4.1.1 Pharmacodynamic Property *(39) (40)*

The pharmacodynamic property was considered as described in section 4.2.1.1.

4.4.1.1A Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. DM01 blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. DM01 has more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because DM01 does not inhibit ACE, it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of DM01 on blood pressure.

Doses of 2.5 mg to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses >40 mg giving >90% inhibition at 24 hours.

4.4.1.1B Dosage and Administration

Adult Hypertension

The usual recommended starting dose of DM01 is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily. No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40 ml/min) or with moderate to marked hepatic dysfunction. For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), initiate under close medical supervision and give consideration to use of a lower starting dose. DM01 Tablet may be administered with or without food. If blood pressure is not controlled by DM01 tablet alone, a diuretic may be added. DM01 may be administered with other antihypertensive agents.

Pediatric Hypertension (6 to 16 years of age)

For children who can swallow tablets, the usual recommended starting dose is 10 mg once daily for patients who weigh 20 to <35 kg (44 to 77 lb), or 20 mg once daily for patients who weigh ≥35 kg. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to a maximum of 20 mg once daily for patients who weigh <35 kg or 40 mg once daily for patients who weigh ≥35 kg. Children <1 year of age must not receive Tablet for hypertension.

For children who cannot swallow tablets, the same dose can be given using an extemporaneous suspension.

4.4.1.1C Indications

DM01 is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

4.4.1.2 Pharmacokinetic Properties

The pharmacodynamic properties were characterized as described in section 4.2.1.2

4.4.1.2A Absorption

DM01 is rapidly and completely bioactivated by ester hydrolysis to active form during absorption from the gastrointestinal tract. The absolute bioavailability of the drug is approximately 26%. After oral administration, the peak plasma concentration (C_{max}) of the drug is reached after 1 to 2 hours. Food does not affect the bioavailability of drug.

4.4.1.2B Distribution

The volume of distribution of the drug is approximately 17 L. Drug is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma drug concentrations well above the range achieved with recommended doses.

4.4.1.2C Metabolism and Excretion

Following the rapid and complete conversion of DM01 to active form during absorption, there is virtually no further metabolism. Total plasma clearance of the drug is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

The drug appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Drug shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of drug are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

4.4.1.3 Physical Properties

4.4.1.3A Description

The description of DM01 was interpreted as per method as mentioned in section 4.2.1.3A.

DM01 is a white to light yellowish powder or crystalline powder.

4.4.1.3B Micromeritic Properties

1. **Bulk and Tapped Density**

The bulk density was calculated as per the method described in section 4.2.1.3B

Table 4.10: Bulk Density of DM01

Bulk Density(g/ml)	Values
Bulk density	0.297 gm/ml
Tap density	0.495 gm/ml

2. **Compressibility**

The compressibility index was calculated as per the method described in section 4.2.1.3B

Table 4.11: Compressibility of DM01

B. No	Compressibility index	Hausner's Ratio
DM01200813	40.00	1.67

Conclusion: From the above data it was concluded that DM01 exhibited very very poor flow properties as per the criteria given in **table**

4.4.1.3C Particle Size Analysis_

The particle size analysis was carried out as per the method mentioned in section 4.2.1.3C.

Table 4.12: Particle size distribution of DM01

B. No.	AR. No.	D (0.9)
DM01200813	RR0155	9.0
DM01020813	RP0653	9.0

Conclusion: This was representative of the drug substance PSD selected for the final drug product formulation.

4.4.1.3D Aqueous solubility as a function of pH

The solubility study was carried out as per the method described in section 4.2.1.3D.

Table 4.13: pH Solubility profile of DM01

Sr. No.	Medium	Solubility (mg/ml)	Remarks*
1	0.1 N HCl	0.161	Sink condition is achieved
2	0.01 N HCl	0.046	Sink condition not achieved
3	0.01 N HCl + 0.10 %SLS	0.108	Sink condition not achieved
4	0.01 N HCl + 0.25 %SLS	0.146	Sink condition is achieved
5	0.01 N HCl + 0.50 %SLS	0.152	Sink condition is achieved
6	0.01 N HCl + 1.00 %SLS	0.161	Sink condition is achieved
7	Purified Water	0.007	Sink condition not achieved
8	Purified Water + 0.10 %SLS	0.009	Sink condition not achieved
9	Purified Water + 0.25 % SLS	0.033	Sink condition not achieved
10	Purified Water + 0.50 %SLS	0.099	Sink condition not achieved
11	Purified Water + 1.00 % SLS	0.137	Sink condition is achieved
12	Acetate buffer pH 4.5	0.002	Sink condition not achieved
13	Acetate buffer pH 4.5 + 0.10 % SLS	0.027	Sink condition not achieved
14	Acetate buffer pH 4.5 + 0.25 % SLS	0.118	Sink condition not achieved
15	Acetate buffer pH 4.5 + 0.50 % SLS	0.140	Sink condition is achieved
16	Acetate buffer pH 4.5 + 1.00 % SLS	0.147	Sink condition is achieved
17	Phosphate buffer pH 5.5	0.008	Sink condition not achieved
18	Phosphate buffer pH 5.5+ 0.10 %	0.011	Sink condition not achieved
19	Phosphate buffer pH 5.5+ 0.25 %	0.065	Sink condition not achieved
20	Phosphate buffer pH 5.5+ 0.50 %	0.070	Sink condition not achieved
21	Phosphate buffer pH 5.5+ 1.00 %	0.103	Sink condition not achieved
22	Phosphate buffer pH 6.8	0.059	Sink condition not achieved
23	Phosphate buffer pH 7.2	0.110	Sink condition not achieved

***** Sink conditions are achieved if solubility is above 0.133 mg/ml

Conclusion: The pH solubility profile indicated that DM01 had pH dependent solubility. DM01 was poorly soluble in the pH range of 4.5-7.2, but solubility was increased in presence of surfactant.

4.4.1.3E Hygroscopicity studies

The hygroscopicity study was carried out as per the method described in section 4.2.1.3E.

Table 4.14: Results for Hygroscopicity of DM01 (API)

Sr. No.	Storage time	Storage condition Results (% water content)	
		30°C/75% RH	25°C/60% RH
1.	Initial	0.47%	
2.	2 Hr	0.48%	0.47%
3.	4 Hr	0.61%	0.47%
4.	8 Hr	0.51%	0.57%
5.	24 Hr	0.64%	0.48%

Conclusion: DM01 did not exhibit hygroscopicity as % water content increased by less 0.2 % at 30°C /75% RH.

4.4.1.4 Chemical Properties

4.4.1.4A Chemical Analysis of DM01

The chemical analysis of DM01 was carried out as per described in section 4.2.1.4A.

Table 4.15: Chemical Analysis of DM01 (API)

Sr. No.	TEST	DM01	LIMITS
1.	**Description**	White powder	White to light yellowish powder
2.	**Loss on drying**	0.21 %	Not more than 0.50%
3.	**Assay**	99.5%	98.0% - 102.0%
4.	**Related Substances**		
	Impurity-1 (Acid Impurity)	0.040%	NMT 0.15%
	Impurity-2 (Trityl alcohol)	ND	NMT 0.15%
	Impurity-3 (Trityl impuirty)	ND	NMT 0.15%
	Impurity-4 (Styrine)	0.039%	NMT 0.15%
	Any other major individual impurity	0.026%	NMT 0.10%
	Total impurities		

		0.120%	NMT 1.00%

ND – Not detected NMT –Not more than

4.4.1.4B Forced Degradation Data of DM01

The study of was carried out as per the method described in section 4.2.1.4A.

Table 4.16: Forced Degradation Data of DM01 API

Force Degradation Data	Impurity Name						
	Impurity 1(Acid Impurity)	Impurity 2 (Trityl alcohol)	Impurity 3 (Trityl Impurity)	Impurity 4 (Styrine)	Single max. Unknown impurity	Total impurity	% Assay
Unstressed	0.201	ND	ND	0.021	0.025	0.247	99.5
Control UV light (For 10 days)	0.209	ND	ND	0.020	0.023	0.252	100.6
UV light degradation (For 10 days)	0.207	ND	ND	0.020	0.020	0.247	99.6
Heat degradation (At 60°C for 10 days)	0.381	ND	ND	0.023	0.050	0.496	100.7
Oxidation (3% v/v H_2O_2 at 25°C for 5 hour)	11.100	ND	ND	0.021	0.079	11.455	88.0
Water hydrolysis (At 60 °C for 18 hour)	14.484	ND	ND	0.016	0.203	14.860	82.7
Acid hydrolysis (0.1 M HCl at 60°C for 18 hour)	12.317	ND	ND	0.080	0.307	12.853	84.5
Base hydrolysis (0.05 M NaOH	18.988	ND	ND	0.018	0.111	19.139	79.1

at 25°C for 20 minute)							

Conclusion: From the forced degradation results it was concluded that DM01 degraded in presence of Oxygen, Water hydrolysis, Acid hydrolysis and base hydrolysis and formed Impurity 1. Other impurities like Impurity 2, Impurity 3 and Impurity 4 were found to be stable in all degradation conditions. Further API was found to be stable on dry heat and UV light.

4.4.1.5 Biological Property

1. **Partition Coefficient(Log P)**

   The Log P value was found to be is 1.0 at pH 7.0.

2. **Bio-pharmaceutics Classification**

   Based on its solubility across physiological pH DM01 was designated as a low solubility drug substance as shown in **table.** The calculated dose solubility volume is as follows: 40 mg (highest strength) / (0.002 mg/ml) = 20000 ml > 250 ml. Therefore, DM01 was considered a BCS Class II compound (low solubility and high permeability) according to the BCS guidance.

4.4.1.6 Drug-Excipient Compatibility Study

The study was carried out as per the method described in section 4.2.1.5.

Table 4.17: Results of Compatibility Study

DM01 Compatibility Study – 4 week, 40°C/75%RH, Open glass vials

Sample	DM01		DM01 + HPC		DM01 + Ferric oxide yellow		DM01 + Mg. Stearate		DM01 + Lactose Monohydrate	
Ratio	As such		1:0.5		1:0.1		1:0.2		1:6	
Impurity	Initial	4 week	Initial	4 week	Initial	4 week	Initial	4 week	Initial	4 week
Impurity-1	0.024	0.017	0.057	0.060	0.064	0.048	0.078	0.067	0.109	0.075
Impurity-2	Not detected									
Impurity-3										
Impurity-4	0.037	0.040	0.037	0.037	0.037	0.038	0.035	0.040	0.034	0.041
% Unknown single maximum impurity	0.013	0.018	0.013	0.023	0.012	0.014	0.013	0.017	0.013	0.020
% Total unknown impurity	0.036	0.071	0.035	0.089	0.034	0.065	0.040	0.080	0.033	0.074
% Total Impurity	0.097	0.128	0.129	0.186	0.135	0.151	0.153	0.187	0.176	0.190
Assay	99.90	99.87	99.87	99.81	99.87	99.85	99.85	99.81	99.82	99.81

Table 4.18: Results of Compatibility Study
DM01 Compatibility Study – 4 week, 40°C/75%RH, Open glass vials

Sample	DM01 + MCC		DM01 + L - HPC		DM01 + Purified Talc		DM01 + Titanium dioxide		DM01 + HPMC	
Ratio	1:2		1:2		1:0.1		1:0.1		1:0.2	
Impurity	Initial	4 week	Initial	4 week	Initial	4 week	Initial	4 week	Initial	4 week
Impurity-1	0.092	0.085	0.113	0.088	0.027	0.083	0.034	0.057	0.040	0.070
Impurity-2	Not Detected									
Impurity-3										
Impurity-4	0.039	0.038	0.052	0.042	0.038	0.040	0.034	0.032	0.037	0.039
% Unknown single maximum impurity	0.013	0.025	0.024	0.019	0.013	0.019	0.011	0.016	0.013	0.015
% Total unknown impurity	0.041	0.087	0.047	0.074	0.034	0.065	0.056	0.049	0.045	0.059
% Total Impurity	0.172	0.210	0.212	0.204	0.099	0.188	0.124	0.138	0.122	0.168
Assay	99.83	99.79	99.79	99.80	99.90	99.81	99.88	99.86	99.88	99.83

Table 4.19: Results of Compatibility Study
DM01 Compatibility Study – 4 week, 40°C/75%RH, Open glass vials

Sample	DM01+ SLS		DM01 +		DM01 + Ferric oxide yellow	
Ratio	As such		1:0.5		1:0.1	
Impurity	Initial	4 week	Initial	4 week	Initial	4 week
Impurity-1	0.024	0.020	0.057	0.032	0.064	0.056
Impurity-2	Not detected					
Impurity-3						
Impurity-4	0.037	0.036	0.037	0.032	0.037	0.034
% Unknown single maximum impurity	0.013	0.013	0.013	0.013	0.012	0.014
% Total unknown impurity	0.036	0.040	0.035	0.039	0.034	0.053
% Total Impurity	0.097	0.096	0.129	0.103	0.135	0.143
Assay	99.90	99.90	99.87	99.90	99.87	99.86

Conclusion: The results indicated that there was no significant change in the description and the levels of impurities in the blends studied, as compared to the initial. Further stability of final dosage form shall be conducted in proposed packing configuration, to conclude compatibility.

4.4.2 Characterization of Reference Product

The characterization of reference product was performed as per the method described in section 4.2.3.

4.4.2.1 Physical Characterization of Reference Product

Table 4.20: Physical Characterization Tablet 40 mg (Reference Product)

Sr No	Strength	40 mg
(d)	Label Claim	Each tablet contain: DM01 tablets 40 mg
(e)	Dosage Form	Film coated Tablets
(f)	Batch. No	186489
(g)	Exp Date	09/15
(h)	Shelf life	24 Month
(i)	Indications	Antihypertensive

Sr No	Strength	40 mg
(j)	Inactive	Hydroxypropylcellulose, Hydroxypropylmethylcellulose, Lactose monohydrate, Low-substituted hydroxypropylcellulose, Magnesium stearate, Microcrystalline cellulose, Talc, Titanium dioxide.
(k)	Tablet Description	White, oval-shaped, film-coated, non-scored tablets
(l)	Tablet Shape	Oval
(m)	Tablet Dimensions	15.18 X 7.11 mm
(n)	Avg. Weight	440.0 mg
(o)	Thickness	4.81 mm
(p)	Hardness	202 N
(q)	Disintegration Time	3 min 10 sec
(r)	Disintegration	Erosion

4.4.2.2 Chemical Characterization of Reference Product

The reference product tablets 40 mg were evaluated for chemical characteristics i.e., Assay and related substances. The results are tabulated in **table**

Table 4.21: Chemical Characteristics of 40 mg

Sr. No	Tests	40 mg
	A.R No.	**DP14/043**
	Batch No. **Exp. Date**	0000963 11/2015
1.	**Assay (%)**	100.2%
2.	Related Substances (s) (Impurity 1) (t) Single maximum unknown impurity **(u)** Total Impurities	0.354% 0.029% 0.383%

4.4.2.3 In-vitro Dissolution Studies of Reference Product

Dissolution Profile of RLD Tablets 40 mg

Medium : 0.1 N HCl, 0.05 M Phosphate buffer, pH 6.8 and Acetate Buffer pH 4.5

Volume : 900 ml

Apparatus : Type II (Paddle)

RPM : 50 RPM

Table 4.22: Dissolution Profile of Reference Product

Cumulative % drug dissolved			
Time (min)	**0.1 N HCl**	**0.05 M Phosphate buffer, pH 6.8**	**Acetate Buffer, pH 4.5**
5	47	44	5
10	95	64	8
15	98	71	9
20	100	74	10
30	101	79	10
45	101	83	11
60	101	85	11

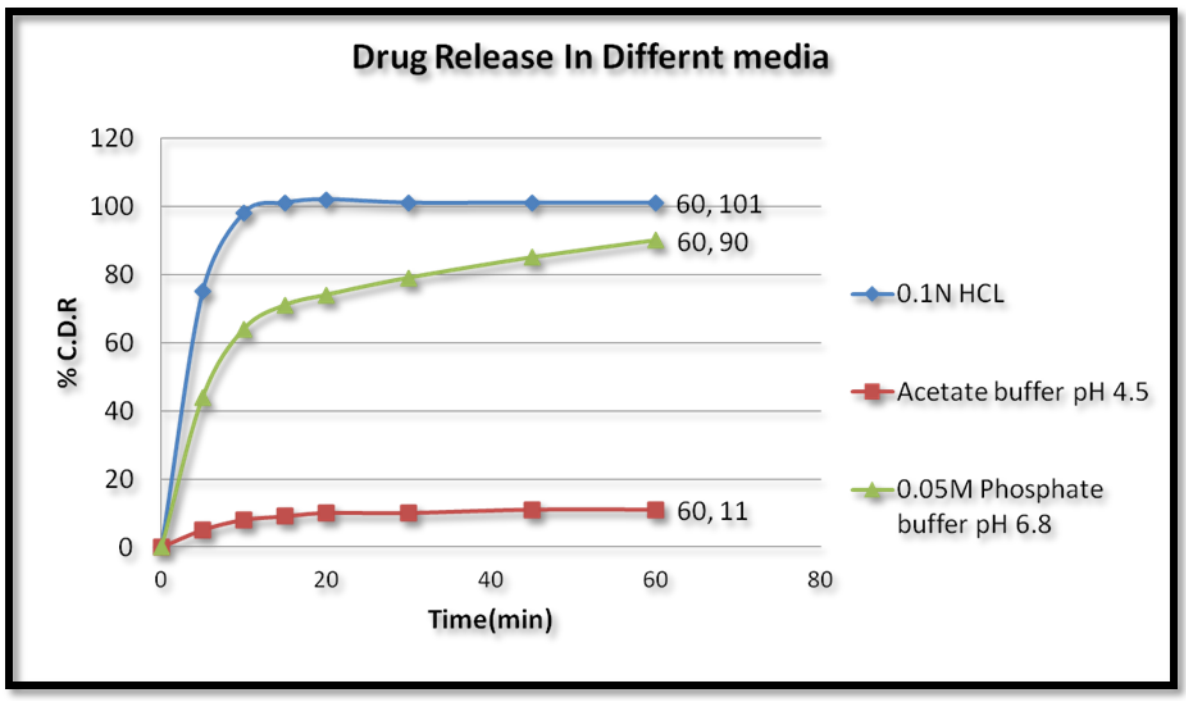


Figure 4.1: RLD dissolution profile

Conclusion:

Similar and complete release profile was observed in 0.1 N HCl for all strengths of RLD. In Acetate buffer pH 4.5, release profiles for all strengths are very slow and incomplete attributes to its lower solubility at pH 4.5. In Phosphate buffer pH 6.8, release profile for RLD was found to be more than 85% in 45 minutes for all strengths. Hence,phosphate buffer, pH 6.8 was selected as release media which is also recommended OGD media.

4.4.3 Identification of Quality Target Product Profile (QTPP)

The identification of QTPP was carried out as per the method described in section 4.2.4.

Table 4.23: Quality Target Product Profile of DM01 Tablet 40 mg

QTPP Element	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: Same dosage form
Dosage design	Immediate Release Tablet	Immediate release design needed to meet label claims
Appearance	Tablet conforming to description, shape and size.	Require to match RLD. Needed for patient acceptability.
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength	5 mg, 20 mg and 40 mg	Pharmaceutical equivalence requirement: Same strength
Stability	24-month shelf-life at room temperature.	Needed for commercialization.
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Meeting the same or compendia or other applicable (quality) standards (i.e., identity, dissolution ,assay, purity, and quality)
	Average weight	
	Identification	
	Assay	
	Uniformity of Dosage Units	
	Dissolution	
	Degradation product	
	Loss on Drying	
	Microbial Limits	
	Residual solvents	

4.4.3 Identification of Critical Quality Attributes

The identification of QTPP was carried out as per the method described in section 4.2.4.

Table 4.24: Critical and Non Critical quality attributes of the DM01 Tablet 40 mg

Critical and non-critical quality attributes of the DM01 Tablet 40 mg				
Drug Product Quality Attributes		**Target**	**Is it critical?**	**Justification of Criticality**
Physical Attributes	Appearance	Color and shape acceptable to the patient and similar to RLD. No visual defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to develop product with color, shape, and appearance similar to RLD and ensure patient acceptability.
	Odor	No unpleasant odor	No	Odor can affect patient acceptability and lead to complaints. For this product, neither the drug substance nor the excipients have an unpleasant odor.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Scoring	Non-Scored	No	The RLD is an un-scored tablet; therefore, the generic tablet will be made in line with RLD as Non-Scored.
Average Weight of Tablets		**40 mg:** 430.4 mg ± 3% (417.5 mg to 443.3 mg)	No	Formulation and process variables are unlikely to impact this CQA.
Identification		Positive for DM01	No	Both formulation and process unlikely impact the identity.

Loss on Drying	Not more than 6.0% w/w	Yes	Moisture content will affect degradation and microbial growth of the drug product and can be a potential CQA.
Dissolution	Similar drug release profile as RLD using OGD recommended release media.	Yes	Both formulation and process affect drug release. Failure to meet the dissolution specification can impact bioavailability. So, it is critical to meet this specification and match drug release profile to RLD.
Related Substances	1.Impurity 1 : NMT 1.5 % 2.Single maximum unknown impurity :NMT 0.2 % 3.Total impurities : NMT 2.0 % (at shelf life)	Yes	Degradation products can impact safety and must be controlled based on compendial/ICH requirements or RLD characterization to limit patient exposure till shelf life.
Assay	90.0% to 110.0% of label claim at shelf life	Yes	Formulation composition and process may affect the assay value of drug product and same will affect safety and efficacy.
Content Uniformity	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process affect content uniformity.
Residual solvent	USP <467> compliance	No	The drug substance and excipients used in the drug product formulation contain residual solvents. The limit is critical to drug product safety. However, organic solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 2.

Conclusion:

During pharmaceutical development all attributes in the QTPP were monitored. The following drug product CQAs were identified for explicit tracking in risk assessment:

Assay, Degradation Products / Impurities, C.U, Dissolution. The criteria for inclusion in this list of CQAs were that these attributes had the greatest potential to be altered by process parameters or formulation variables.

4.4.4 Risk Assessment of Drug Substance Attributes on Drug Product CQAs

The risk assessment of the drug substance attributes was carried out as per the method described in section 4.2.6.4.

Table 4.25: Initial risk assessment of the drug substance attributes

Initial Risk Assessment of the Drug Substance Attributes									
Drug Product CQAs	**Polymorphism**	**Size Distribution**	**Hygroscopicity**	**Solubility**	**Moisture Content**	**Solvent Content**	**Process Imp.**	**Chem. Stability**	**Flow Property**
Assay	Low	Low	Low	Low	Low	Low	Low	High	Low
Uniformity of Dosage units	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	High	Low	High	Low	Low	Low	Low	Low
Degradation Products	Low	Low	Low	Low	High	Low	High	High	Low

Table 4.26: Justification for the initial risk assessment of the drug substance attributes.

Drug Substance Attributes	Drug Product CQAs	Justification
Polymorphism	Assay	Drug substance solid state form does not affect tablet assay and content uniformity. The risk is low.
	Content Uniformity	
	Dissolution	Different polymorphic forms of the drug substance have different solubility and can impact tablet dissolution. DM01 USP exhibits polymorphism; based on X-Ray diffraction studies, it is concluded that the manufacturing process followed manufacturer consistently produces the prior art crystalline Form. The risk is low.
	Degradation Products	Drug substance with different polymorphic forms may have different chemical stability and may impact the degradation products of the drug product. Since DM01 USP exhibits polymorphism; based on X-Ray diffraction studies, it is concluded that the manufacturing process followed by manufacturer consistently produces the prior art crystalline Form. The risk is low.
Particle Size Distribution (PSD)	Assay	Based on the drug substance characterization API exhibit poor flow characteristics which may impact on assay and uniformity of dosage units. Micronized API was selected.
	Content Uniformity	

	Dissolution	The drug substances belong to low solubility criteria as per BCS classification. Thus, particle size of drug substances may impact on solubility rate & dissolution rate of drug product so considered at high risk for dissolution.
	Degradation Products	The drug substance is stable as per DMF. The risk is low.
Hygroscopicity	Assay	DM01 is not hygroscopic. So the risk is low.
	Content Uniformity	
	Dissolution	
	Degradation Products	

Drug Substance Attributes	Drug Product CQAs	Justification
Solubility	Assay	Solubility does not affect tablet assay, Uniformity of Dosage Units and degradation products. Thus, the risk is low.
	Content Uniformity	
	Degradation Products	
	Dissolution	DM01 is BCS class II drug and exhibits low solubility across the physiological pH range. Drug substance solubility strongly impacts dissolution. The risk is high. The formulation and manufacturing process will be design to mitigate this risk.
Moisture Content	Assay	Moisture is controlled in the drug substance specification (NMT 0.5%). Thus, it is unlikely to impact assay, Uniformity of Dosage Units and dissolution. The risk is low.
	Content Uniformity	
	Dissolution	
	Degradation Products	The drug substance is sensitive to moisture based on forced degradation studies. The risk is high.
Residual Solvents	Assay	Residual solvents are controlled in the drug substance specification and At ppm level; residual solvents are unlikely to impact product CQAs. The risk is low.
	Content Uniformity	
	Dissolution	
	Degradation Products	
Process Impurities	Assay	Know, unknown and total impurities are controlled in the drug substance specification as per pending USP monograph and ICH Q3A limits. Within this range, process impurities are unlikely
	Content Uniformity	
	Dissolution	

		to impact assay CU, and dissolution. The risk is low.
	Degradation Products	There may be an impact of process impurity of on degradation products formed in drug product so excipient compatibility study needs to be done to study the effect between process impurities and commonly used drug product excipients. The risk is high.
Chemical Stability	Assay	The drug substance is susceptible to acid hydrolysis, base hydrolysis and oxidative degradation; therefore, drug substance chemical stability may affect drug product assay and degradation products. The risk is high.
	Degradation Products	
	Content Uniformity	Tablet CU is mainly impacted by powder flowability and blend uniformity. Tablet CU is unrelated to drug substance chemical stability. The risk is low.
	Dissolution	Tablet dissolution is mainly impacted by drug substance solubility and particle size distribution. Tablet dissolution is unrelated to drug substance chemical stability. The risk is low.
Flow Properties	Assay	DM01 has poor flow properties. In extreme cases, poor flow may impact assay and content uniformity. Thus, wet granulation approach is to be selected
	Content Uniformity	
	Dissolution	The flowability of the drug substance is not related to its degradation pathway . Therefore, the risk is low.
	Degradation Products	

Updated Risk Assessment of API Attributes on Drug Product CQAs

Acceptable ranges for the high risk of drug substance attributes had been established and are included in the control strategy. The risk assessment of the drug substance attributes was updated as given in table below with justifications provided.

Table 4.27: Updated risk assessment of the drug substance attributes

Initial Risk Assessment of the Drug Substance Attributes									
Drug Product CQAs	**Polymorphism**	**Particle Size Distribution**	**Hygroscopicity**	**Solubility**	**Moisture Content**	**Solvent Content**	**Process Imp.**	**Chem. Stability**	**Flow Property**
Assay	Low	Low	Low	Low	Low	Low	Low	Low*	Low
Uniformity of Dosage units	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low *	Low	Low*	Low	Low	Low	Low	Low
Degradation Products	Low	Low	Low	Low	Low*	Low	Low*	Low*	Low

*** reduced risk**

Table 4.28: Justification for the reduced risks of the drug substance attributes

Drug Substance Attributes	Drug Product CQAs	Justification
Particle Size Distribution (PSD)		
	Dissolution	Micronized API having $d_{0.9}$: Less than 10 µm was selected based on prior development. So the risk is low.
Solubility	Dissolution	A drug substance is BCS class II and exhibit low solubility across the physiological pH range. Thus micronized API ($d_{0.9}$: Less than 10 µm) is to be selected which has higher solubility. So the risk is low.
Moisture Content	Degradation products	The drug substance is sensitive to moisture content. Thus non aqueous wet granulation is to be selected to mitigate the risk associated with moisture content. So the risk is low.
Process Impurity	Degradation Products	During the excipient compatibility study, no incompatibility between process impurities and commonly used drug product excipients were observed. The risk is low.
Chemical Stability	Assay	Formulation variables, manufacturing process and drug product packing optimized to mitigate risk of chemical stability of drug substance to affect degradation product of drug product. Thus, the risk is low.

Conclusion

The high risk drug substance attributes which could affect the drug product CQAs were reduced to low risk factors because of the reasons given in table 4.28.

4.4.5 Formulation Development

4.4.5.1 Risk Assessment of the Formulation Variables

The risk assessment of the formulation variables was carried out as per the method described in section 4.2.7.1.

Table 4.29: Initial Risk assessment of the Formulation Variables

Initial Risk Assessment of the Formulation Variables			
Drug Product CQAs	Binder Level	Disintegrant Level	Magnesium Stearate Level
Assay	Low	Low	Low
Uniformity of Dosage units	Low	Low	Low
Dissolution	High	High	High
Degradation Products	Low	Low	Low

Table 4.30: Justification of the Initial Risk Assessment of the Formulation Variables.

Formulation Variables	Drug Product CQAs	Justification
Binder Level	Assay	The level of binder used is low and its impact on flow is minimal, it is unlikely to impact assay and Uniformity of Dosage units. The risk is low.
	Uniformity of Dosage units	
	Dissolution	Binder level can impact the granules property and thus disintegration time and ultimately dissolution. Since achieving rapid disintegration is important for a drug product containing a BCS class II compound, the risk is high.
	Degradation Products	Binder is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
Disintegrant Level	Assay	Since the level of Disintegrating Agent used is low and its impact on flow is minimal, it is unlikely to impact. The risk is low.
	Uniformity of Dosage units	
	Dissolution	Disintegrating Agent's level can impact the disintegration time and, ultimately, dissolution. Since achieving rapid disintegration is important for a drug product containing a BCS class II compound, the risk is high.
	Degradation Products	Disintegrating Agent is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
Magnesium Stearate Level	Assay	Since the level of magnesium stearate used is low and its impact on flow is minimal, it is unlikely to impact assay and Uniformity of Dosage units. The risk is low.
	Uniformity of Dosage units	
	Dissolution	Over-lubrication due to excessive lubricant may retard dissolution. The risk is high.
	Degradation Products	Magnesium Stearate is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.

4.4.5.2 Risk Assessment of the Unit Operations

The risk assessment of unit operations was carried out as per the method described in section 4.2.7.1.

Table 4.31: Criticality assessment of unit operations

Sr.No	Unit operation	Is it critical?	Justification
1.	Shifting	No	Shifting is carried out to remove lumps or foreign particles in the materials and thus giving uniform particle size material.
2.	Dry mixing	Yes	Dry mixing is important to achieve homogeneous mass & can affect blend uniformity.
3.	Granulation	Yes	Kneading time is more critical amongst the steps of granulation like binder addition, binder volume etc as the formulation contains maximum lactose which has the property of losing water during kneading.
4.	Wet milling	No	It is done to break lumps formed during wet granulation, so not critical.
5.	Drying	Yes	Higher % of moisture may impact drug product related substances,so it is critical.
6.	Blending	Yes	It may impact blend uniformity,so it is critical.
7.	Lubrication	Yes	Over lubrication may impact dissolution of drug from dosage form,so it is critical.
8.	Compression	Yes	Change in hardness and machine speed during compression may impact dissolution,so it is critical.
9.	Coating	No	Film coating is non-functional so it will not impact the dissolution.

Table 4.32: Quality risk assessment

Sr. No	Unit operations	Effect on CQA's	Risk assessment			Risk category	Remarks
			Severity	Probability	Risk score		
1.	Dry mixing	Content uniformity	1	2	2	Low	Further mixing during granulation & blending will ensure CU
		Related Substances	1	1	1	Low	It will not impact RS
		Dissolution	1	1	1	Low	It will not impact the dissolution of drug product
2.	Granulation	Content uniformity	2	1	2	Low	Predefined dry mixing & subsequent mixing will ensure uniformity.
		Related Substances	1	1	1	Low*	Optimizing the kneading time and keeping the binder addition time,risk to impact related substance and dissolution is lowered.
		Dissolution	1	1	1	Low*	
3.	Drying	Content uniformity	1	1	1	Low	It will not Impact CU
		Related Substances	1	1	1	Low	Drying time and LOD if kept within specified limit,risk is lowered.
		Dissolution	1	1	1	Low	It will not impact dissolution.

Table 4.33: Quality Risk Assessment

Sr. No	Unit operations	Effect on CQA's	Risk assessment			Risk category	Remarks
			Severity	Probability	Risk score		
4.	Blending	Content uniformity	1	1	1	Low*	Based on the CU data at different blending time, risk s high to low within the studied range.
		Related	1	1	1	Low	It will not impact RS
		Dissolution	1	1	1	Low	It will not impact dissolution.
5.	Lubrication	Content uniformity	1	1	1	Low	It involves mixing with very low amount of lubricant so risk is low.
		Related	1	1	1	Low	It will not impact RS.
		Dissolution	1	1	1	Low	Based on dissolution data at different blending time(3-7min), risk will be high to low.
6.	Compression	Content uniformity	1	1	1	Low	Based on CU data at different speed of compression, risk is high to low within the range studied.
		Related	1	1	1	Low*	It will not impact RS.
		Dissolution	1	1	1	Low*	Based on dissolution data at different hardness, risk is high to low for studied range.

***Risk level is reduced from Medium/High to low.**

4.4.5.3 Formulation Methods

4.4.5.3A Tablets prepared by Direct Compression

The tablets were prepared as per the method and formula described in section 4.2.7.2A.

Table 4.34: Evaluation of DM01 tablets by direct compression

Evaluation		4001	4002	4003	4004	4005
	Punch Size	**15 X 7 mm, Oval, Sub-concave**				
1.	**Average weight (mg)**	419	421	420	420	420
3.	**Friability(%)**	<0.1	<0.1	<0.1	<0.1	<0.1
4.	**Disintegration Time (min)**	2.5-3.5	3.0-4.0	1.5-2.0	2.0-2.5	3.5-4.5
5.	**Resistance to crushing (N)**	100-110	100-110	110-130	110-130	110-130

Dissolution of DM01 tablet 40 mg

Medium : 0.05M Phosphate buffer, pH 6.8 Volume : 900 ml

Apparatus : Type II (Paddle)

Table 4.35: Comparative dissolution data

Time	RLD	DC 4001	DC 4002	DC4003	DC4004	DC4005
0	0	0	0	0	0	0
10	74	41	51	50	55	55
15	83	51	59	59	60	61
20	89	54	63	64	65	68
30	96	61	70	72	70	72
45	100	65	80	81	79	85

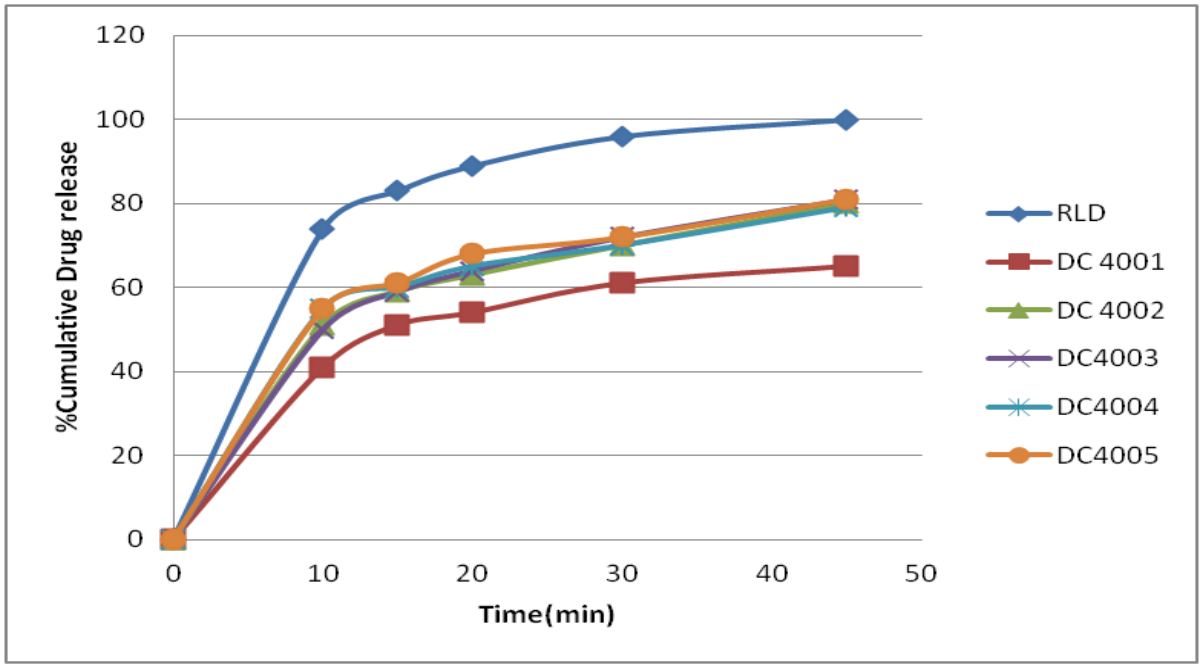


Figure 4.2: Comparative Dissolution Profile of DM01 40mg tablet

Discussion:

The tablets of DM01 manufactured by direct compression were found to be acceptable in all other evaluation parameters except the two most important ones that are dissolution and disintegration. These two parameters are directly and indirectly related to the bioavailability of drug. Different combination of formulation were tried i.e. change in particle size of A.P.I, change in the concentration of binder & disintegrant and that of lubricant. Inspite of the major changes in the formulation variables the key parameter of complete release (85% of drug) was not achieved at 45 min. Thus, the strategy of direct compression was discontinued.

4.4.5.3B Tablets prepared by Wet Granulation

The tablets were prepared as per the method and formula described in section 4.2.7.2B.

Table 4.36: Physical Characteristics of DM01 Tablets 40 mg - GR5001

S. No	Parameter	Observations
	Batch No	**GR5001**
1.	Average weight	420.0 mg
2.	Punch Size	15 X 7 mm, Oval, Sub concave
3.	Thickness	5.00-5.10 mm
4.	Disintegration Time	4-5 min
5.	Resistance to crushing	120-145 N
6.	Friability	Nil

Comparative dissolution profile of DM01 tablets 40 mg

Medium : 0.05M Phosphate buffer, pH 6.8

Volume : 900 ml

Apparatus : Type II (Paddle)

RPM : 50 RPM

Table 4.37: Comparative Dissolution profile of DM01 tablets 40 mg GR5001

	RLD Tablet 40 mg	**DM01 Tablet 40 mg**
Batch No	**0000963**	**GR5001**
Time (min)		
0	0	0
10	63	59
15	71	67
20	76	75
30	80	80
45	88	83

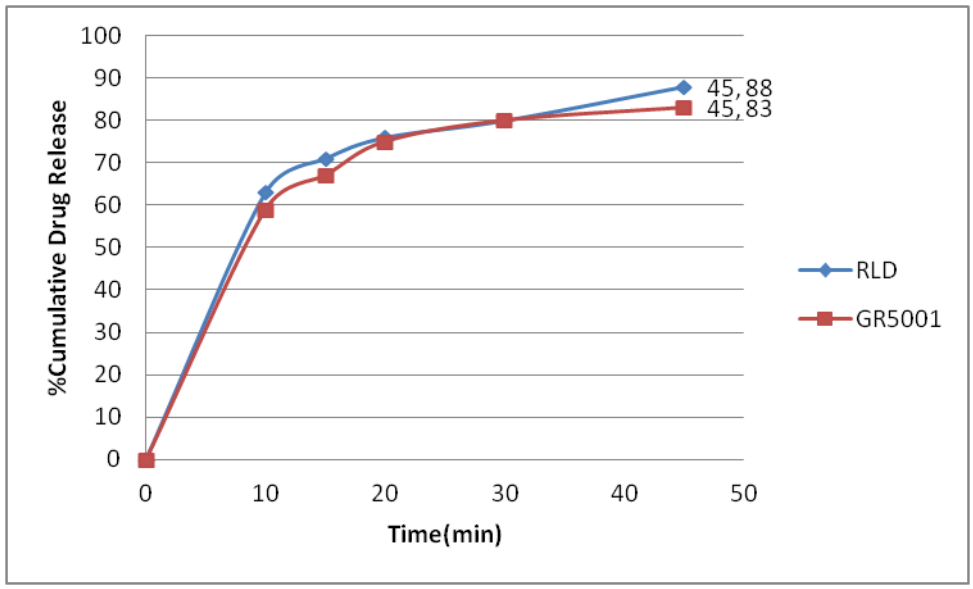


Figure 4.3: Comparative dissolution profile of GR5001 with RLD

Observation: - Process and physical parameters as well as chemical parameters were found satisfactory. The in vitro drug release of DM01 tablets 40 mg and Reference product was found to be similar.

Results of GR5002 to check the reproducibility of GR5001

Table 4.38: Physical Characteristics of DM01 Tablets 40 mg

S. No	Parameter	Observations
	Batch No	ASOMDTG4004
1.	Average weight	420.0 mg
2.	Punch Size	15 X 7 mm, Oval, Sub Concave
3.	Thickness	5.00-5.15 mm
4.	Disintegration Time	4 min-5 min
5.	Resistance to crushing	120-145 N
6.	Friability	Nil

Observation: All the physical parameters were found to be satisfactory. However in few tablets light tendency of sticking was observed.

Comparative dissolution profile of DM01 tablet 40 mg

Medium : 0.05M Phosphate buffer, pH 6.8 Apparatus : Type II (Paddle)

Volume : 900 ml RPM : 50 RPM

Table 4.39: Comparative dissolution profile of DM01 tablet 40 mg GR5002

	RLD Tablet 40 mg	DM01 Tablet 40 mg
Batch No	**0000963**	**GR5001**
Time (min)		
0	0	0
10	63	59
15	71	67
20	76	75
30	80	80
45	88	83

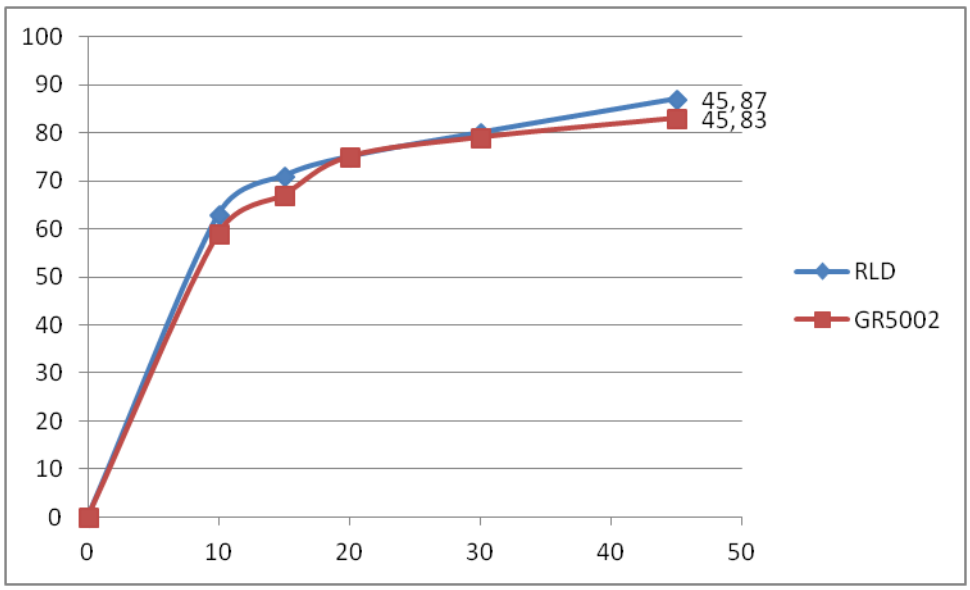


Figure 4.4: Comparative dissolution profile of GR5001 with RLD

Discussion:

The drug release of DM01 tablet 40 mg batch GR5002 was found to be similar to RLD Batch no 0000963 as well that of GR5001.Based on the development work shown above, all the process, physical parameters were found to be satisfactory. Thus, wet granulation

strategy was finalized for optimization by DoE to get an optimized region in the design space.

4.4.5.4 Formulation Optimization

The formulation optimization was carried out by Box-behnken design as per the method mentioned in section 4.2.7.2.

File Version : 8.0.7.1 **Study Type : Response Surface**
Design Type : Box-Behnken **Design Model : Quadratic**
Run : 12+5 center points **Blocks : No Blocks**

Table 4.40: Summary of the factors and responses studied.

3 level Box-Behnken DoE		Levels		
		-1	0	+1
A	Binder Concentration (% w/w)	2.4	3.6	4.8
B	Disintegrant Concentration (EG) (% w/w)	2.8	4.8	6.8
C	Kneading Time(sec)	30	60	90

Response	Goal	Acceptable Ranges
Dissolution @ 45 min	Maximize	NLT 85 %
Disintegration Time	In range	5-7

RUNS	FACTORS			RESPONSES	
	Binder %	Disintegrant %	Kneading time(sec)	Disintegration time(min)	Dissolution %
1	1	0	-1	13	83
2	0	0	0	3.5	88
3	0	0	0	4	90
4	-1	0	1	2	86
5	1	0	1	13	86
6	0	0	0	3.5	89
7	0	-1	-1	5	82
8	1	-1	0	9	83
9	-1	0	0	4	88
10	1	0	1	5	88
11	0	-1	0	1	90
12	1	-1	0	8	87
13	0	1	1	1.5	87
14	-1	0	-1	2	80
15	-1	1	0	1.5	87
16	0	0	0	3.5	89
17	0	1	-1	6	86

Table 4.41: Unit Composition of DM01 40 mg optimization trials

Sr. No	Batch No.	G4001	G4002	G4003	G4004	G4005	G4006	G4007	G4008	G4009
	Ingredients	**Qty/Tab (mg)**								
Dry mixing										
1.	DM01	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
2.	LACTOSE MONOHYDRATE	240.80	245.80	245.80	240.80	240.80	245.80	254.04	249.04	250.80
3.	HPC (Klucel EXF)	20.00	15.00	15.00	10.00	20.00	15.00	15.00	20.00	10.00
4.	L-HPC (LH-21)	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
5.	MCC (AVICEL PH 101)	35.00	35.00	35.00	35.00	35.00	35.00	35.00	35.00	35.00
Granulation										
6.	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Lubrication										
7.	MCC (AVICEL PH 101)	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
8.	L-HPC (LH-21)	20.00	20.00	20.00	20.00	20.00	20.00	11.76	11.76	20.00
9.	Magnesium stearate	4.20	4.20	4.20	4.20	4.20	4.20	4.20	4.20	4.20
Theoretical weight (mg)		420.00	420.00	420.00	420.00	420.00	420.00	420.00	420.00	420.00

Table 4.42: Unit Composition of DM01 40 mg optimization trials

Sr. No	Batch No.	G4010	G4011	G4012	G4013	G4014	G4015	G4016	G4017
	Ingredients	**Qty/Tab (mg)**							
Dry mixing									
1.	DM01	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
2.	LACTOSE MONOHYDRATE	240.80	254.04	249.04	250.80	245.80	259.04	232.24	245.80
3.	HPC (Klucel EXF)	20.00	15.00	20.00	15.00	10.00	10.00	15.00	15.00
4.	L-HPC (LH-21)	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
5.	MCC (AVICEL PH 101)	35.00	35.00	35.00	35.00	35.00	35.00	35.00	35.00
Granulation									
6.	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Lubrication									
7.	MCC (AVICEL PH 101)	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
8.	L-HPC (LH-21)	28.56	20.00	11.76	28.56	20.00	28.56	20.00	28.56
9.	Magnesium stearate	4.20	4.20	4.20	4.20	4.20	4.20	4.20	4.20
Theoretical weight (mg)		420.00	420.00	420.00	420.00	420.00	420.00	420.00	420.00

Table 4.43: Physical Characteristics of DM01 Tablets 40 mg

B.No.		G4001	G4002	G4003	G4004	G4005	G4006
Punch Size		15 X 7 mm, Oval, Sub Concave					
1.	Average weight (mg)	422.5	420.8	421.2	420.3	419.8	419.2
2.	Thickness (mm)	5.0-5.10	5.0-5.15	5.0-5.15	5.0-5.1	5.0-5.15	5.0-5.15
3.	Disintegration Time(min)	13	3.5	4	2	13	3.5
4.	Resistance to crushing (N)	120-150	120-140	130-150	120-150	130-150	120-150

B.No.		G4007	G4008	G4009	G4010	G4011	G4012
Punch Size		15 X 7 mm, Oval, Sub Concave					
1.	Average weight (mg)	419.7	420.4	421.7	419.7	421.3	419.7
2.	Thickness (mm)	5.0-5.15	5.0-5.15	5.0-5.15	5.0-5.10	5.0-5.10	5.0-5.10
3.	Disintegration Time(min)	5	9	4	5	1	8
4.	Resistance to crushing (N)	120-140	120-150	120-150	130-155	120-150	120-150

B.No.		G4013	G4014	G4015	G4016	G4017
Punch Size		15 X 7 mm, Oval, Sub Concave				
1.	Average weight (mg)	420.4	421.7	422.5	420.8	421.2
2.	Thickness (mm)	5.0-5.15	5.0-5.15	5.0-5.1	5.0-1.5	5.05-5.10
3.	Disintegration Time (min)	1.5	2	1.5	3.5	6
4.	Resistance to crushing (N)	120-140	130-150	120-150	130-150	120-150

Design Interpretation

Based on the sum of squares of sequential models (i.e., linear, two factor interaction, quadratic and cubic), the highest order polynomial model was selected where the additional terms were significant and the model was not aliased. The model terms were further reduced based on the significance level (α = 0.05) using the backward model selection method.

Sum of squares

Table 4.44: Sequential Model Sum of Squares [Type I] for response 1

Sequential Model Sum of Squares [Type I]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Mean vs Total	82391.27	1	82391.27			
Linear vs Mean	41.66667	2	20.83333	5.365854	0.0333	
2FI vs Linear	0.25	1	0.25	0.056799	0.8185	
Quadratic vs 2FI	25.9378	2	12.9689	13.30742	0.0099	Suggested
Cubic vs Quadratic	2.833333	2	1.416667	2.083871	0.2708	Aliased
Residual	2.039474	3	0.679825			
Total	82464	11	7496.727			

Table 4.45: Sequential Model Sum of Squares [Type I] for response 2

Sequential Model Sum of Squares [Type I]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Mean vs Total	1.290E+005	1	1.290E+005			Suggested
Linear vs Mean	15.00	3	5.00	1.28	0.3223	
2FI vs Linear	14.75	3	4.92	1.37	0.3089	
Quadratic vs 2FI	28.71	3	9.57	9.18	0.0080	Suggested
Cubic vs Quadratic	4.50	3	1.50	2.14	0.2376	Aliased
Residual	2.80	4	0.70			
Total	1.290E+005	11	7953.35			

ANOVA table for the significant terms is summarized in the below table.

Table 4.46: ANOVA for Response Surface Quadratic Model for response 1

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	8.55	9	0.95	13.92	0.0011	significant
A-Binder	7.25	1	7.25	106.16	<0.0001	
B-Disintegrant	0.067	1	0.067	0.99	0.3537	
C- Kneading	0.24	1	0.24	3.25	0.1028	
AB	0.068	1	1.00	0.3501		
AC	0.000	1	0.000	1.000		
BC	0.48	1	7.04	0.0328		
A^2	0.020	1	0.30	0.6012		
B^2	0.18	1	2.60	0.1509		
C^2	0.27	1	3.95	0.0871		
Residual	0.48	7	0.068			
Lack of Fit	3.122807	4	0.780702	0.78070	0.6284	not significant
Pure Error	0.021	4	5.349E-003			
Cor Total	9.03	16				

The Model F-value of 13.92 implies the model is significant. There is only a 0.11% chance that an F-value this large could occur due to noise.Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, BC are significant model terms.Values greater than 0.1000 indicate the model terms are not significant.

The "Lack of Fit F-value" of 28.45 implies the Lack of Fit is significant. There is only a 0.37% chance that a "Lack of Fit F-value" this large could occur due to noise.

Final Equation in Terms of coded Factors:(Response 1)

$Y = 1.31+0.95*A- 0.092*B -0.17*C-0.13*AB-1.629E-017*AC-0.35*BC+0.07*A^2 - 0.21*B^2 +0.25*C^2$

Table 1.47: ANOVA for Response Surface Quadratic Model for response 2

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	58.46	9	6.50	6.50	0.0124	significant
A-Binder	12.50	1	12.50	11.99	0.0105	
B-Disintegrant	0.50	1	0.50	0.48	0.5110	
C- Kneading	2.00	1	2.00	1.92	0.2086	
AB	12.25	1	11.75	0.011		
AC	2.25	1	2.16	0.1853		
BC	0.25	1	0.24	0.6394		
A^2	17.27	1	16.56	0.0048		
B^2	2.632E-003	1	2.523E-003	0.9613		
C^2	9.79	1	9.39	0.0182		
Residual	7.30	7	1.04			
Lack of Fit	4.50	3	1.50	2.14		Not significant
Pure Error	2.80	4	0.70			
Cor Total	65.76	16				

The Model F-value of 6.23 implies the model is significant. There is only a 1.24% chance that an F-value this large could occur due to noise.Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, AB, A^2, C^2 are significant model terms.

Final Equation in Terms of coded Factors:(Response 2)

$Y = 88.80-1.25*A-0.25*B +0.50*C+1.75*AB+0.75*AC-0.25*BC-2.03*A^2 - 0.025*B^2 -1.52*C^2$

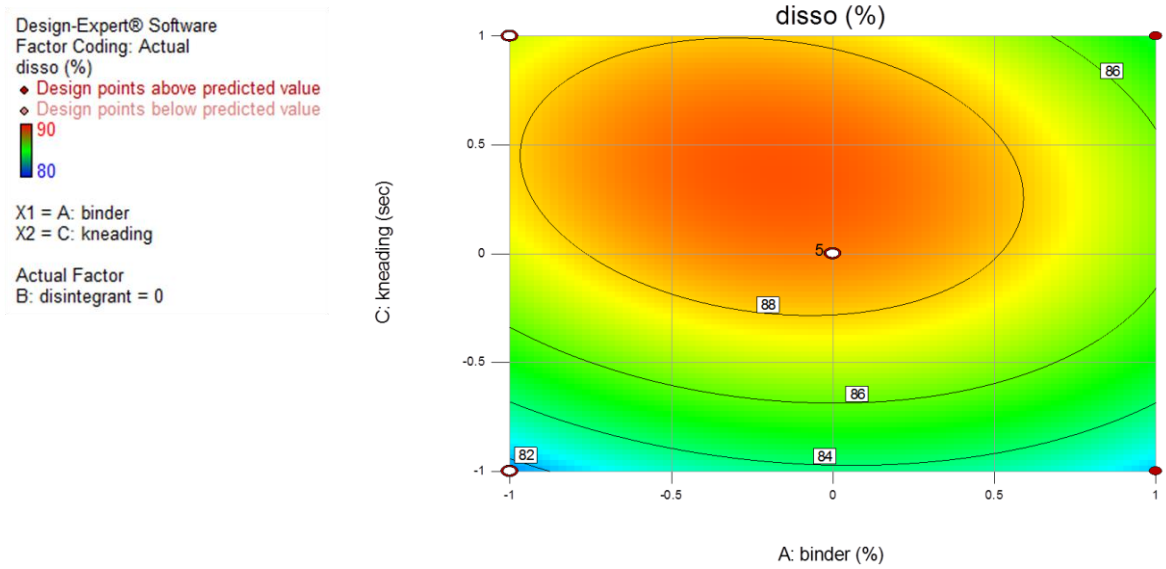


Figure 4.5: 2-D Contour Plot response 1

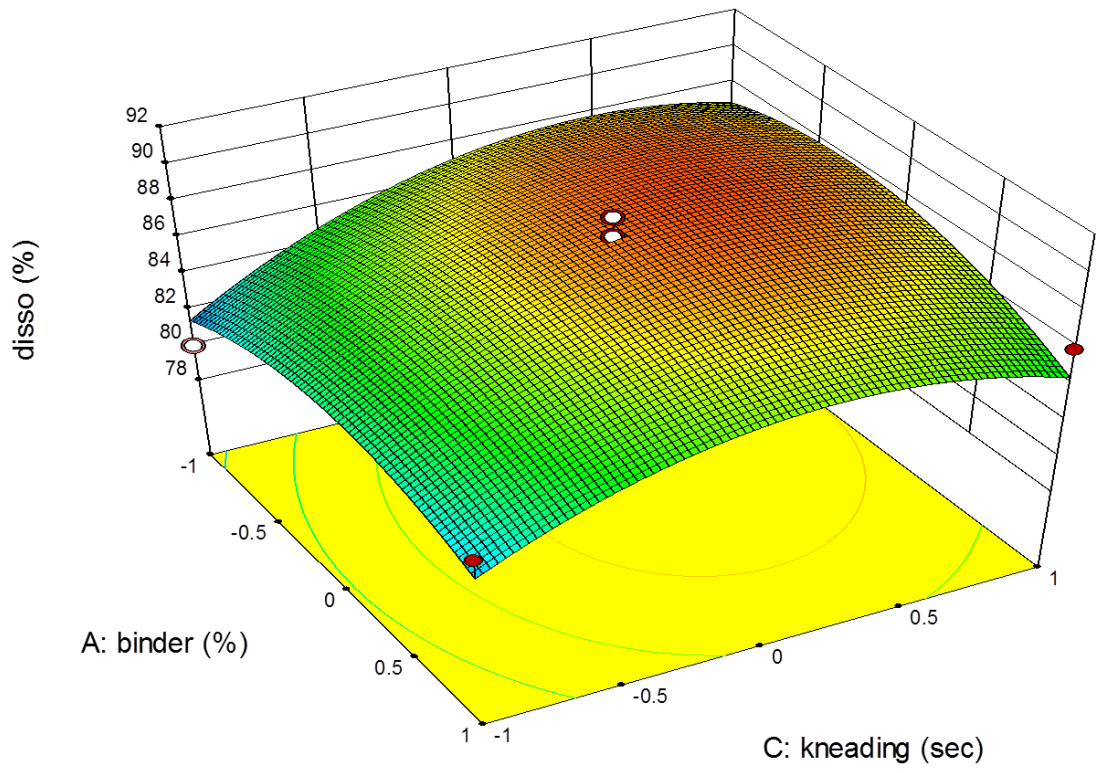


Figure 4.6: 3-D contour plot for response 1

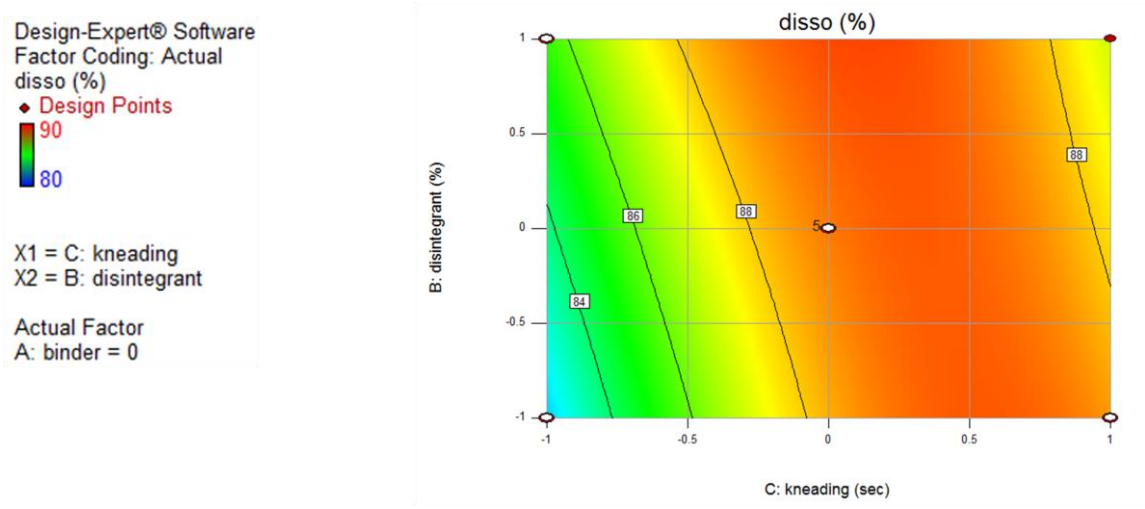


Figure 4.7: 2-D Contour Plot response 2

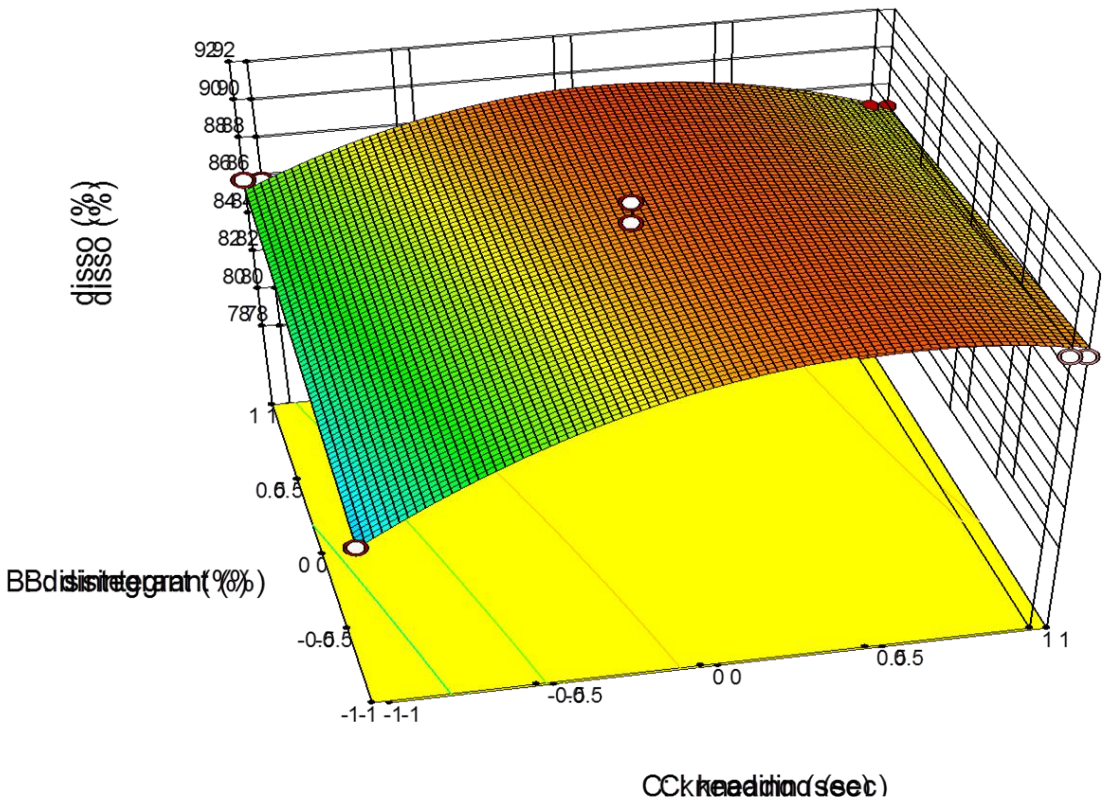
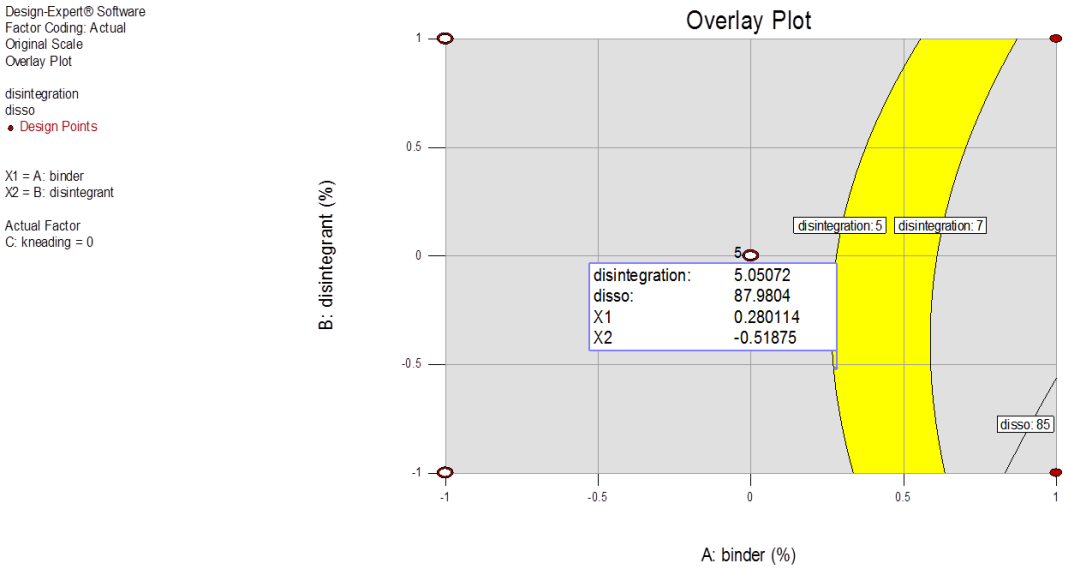


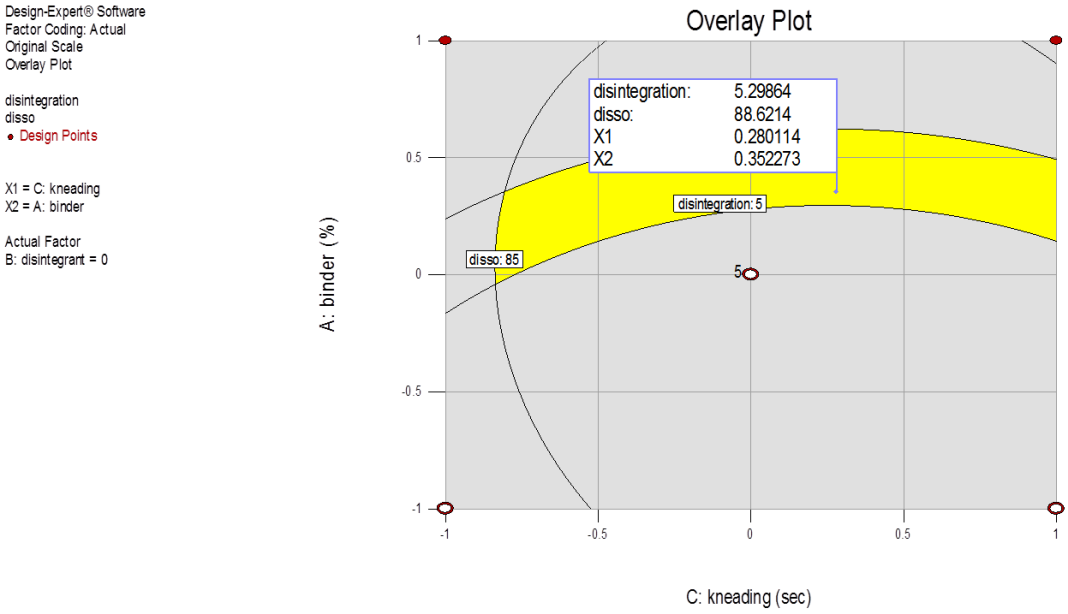
Figure 4.8: 3-D contour plot for response 2

Overlay plots for the design:

1) Keeping kneading constant



2) Keeping disintegrant constant



Interpretation

The relationship between dependent and independent variables was further elucidated using response contour plots as shown in figure above. It is clearly shown that the relationships among the two variables are non-linear because of the curved contour lines.
It was found that at a fixed disintegrant level increasing binder level resulted in an increasing dissolution. Within 2.8 to 5.8 % of disintegrant concentration binder had a greater impact on the dissolution. In this range of disintegrant, lower level of binder (2.4 %) had negative impact and dissolution was observed less than 85 % and however further increasing the binder level increasing the dissolution. Kneading time had significant impact on dissolution as well as on disintegration

At higher level of disintegrant, binder level had no major impact on dissolution. And dissolution varies from minimum 86 % to 90 % as binder increased from lower to higher level. Nevertheless within the studied range of binder and disintegrant, predefined criterion of dissolution and disintegration was apt.

The design space was determined from overlay plot for dissolution response of studied multifactor. The overlay region is comprised of the ranges for binder and disintegrant. The entire yellow zone of the overlay plot indicates the predefined criteria for dissolution (NLT 85 % at 45 min) and disintegration (5-7min)was met within the ranges studied for both formulation variables.
In order to validate the RSM results, further one experiment in which both formulation variables were in the ranges of the design space have been carried out. The selected level of binder, disintegrant and kneading time were 3.80%, 3.46% and 31.5 sec respectively. The manufacturing process was kept similar as defined in batch no G4001. The physical parameters of the tablets were found to be satisfactory and the tablets were evaluated for the dissolution.The experimental and predicted values of the response variable were presented in the table below.

Table 4.48: Results of Design space validation study

Time	Rt	Tt	{Rt-Tt}	$(Rt-Tt)^2$
10	63	59	4	16
15	71	67	4	16
20	76	75	1	1
30	80	80	0	0
45	88	87	1	1

sum (Rt-Tt)	10
sum $(Rt-Tt)^2$	34
sum Rt	378
Similarity factor f 2	78
Difference factor f1	3

Where, Rt is cumulative % dissolved of reference product at time t.

Tt is cumulative % dissolved of test product at time t.

Response	**Batch No:G4025**	**Predicted Value**
	Actual Value	**CI low**
Dissolution @ 45 min	87 %	86.02

From the results, it is shown that the actual value is higher than the lower CI (Confidence Interval) of the responses. The high degree of prediction obtained from check point experiment has shown the reliability and effectiveness using 3-level Box-behnken design using RSM to study the formulation variables having high impact on the product CQA i.e dissolution and disintegration.

Table 4.49: Selected Level for the formulation variables

Formulation variables	**Target**
Binder Level	3.80 %
Disintegrant Level	3.46%
Kneading time	31.5 sec

2.2.1.5 Updated Risk Assessment of the Formulation Variables

Based on the results of the formulation development studies the initial risk assessment of the formulation variables was updated in Table 59 with justifications in Table 60

Table 4.50: Updated Risk Assessment of the Formulation Variables

Updated Risk Assessment of the Formulation Variables			
Drug Product CQAs	**Binder Level**	**Disintegrant Level**	**Magnesium Stearate Level**
Assay	Low	Low	Low
Uniformity of Dosage units	Low	Low	Low
Dissolution	Low*	Low*	Low*
Degradation Products	Low	Low	Low

Table 4.51: Justification for the reduced risks of the formulation variables

Formulation Variables	Drug Product CQAs	Justification
Binder Level	Dissolution	The risk is reduced from high to low. Within the range studied, tablets demonstrated acceptable dissolution.
Disintegrant Level	Dissolution	The risk is reduced from high to low. Within the range studied, levels of Disintegrant affect the disintegration time. However dissolution was not affected. So the risk reduced to low.
Magnesium Stearate Level	Dissolution	Effect of Magnesium Stearate on dissolution was studied in initial prototype trials. By increasing the lubricant level from 0.5% to 1 % dissolution was not affected.. So risk is reduced to low.

4.4.5.5 Manufacturing Process Optimization

Table 4.52: Initial risk assessment of the manufacturing process for DM01 Tablet 40mg

Initial risk assessment of the manufacturing process for DM01 Tablets 40 mg						
Drug Product CQAs	**Dry mixing**	**Granulation**	**Drying**	**Milling**	**Blending & Lubrication**	**Compression**
Assay	Low	Low	Low	Low	High	Low
Uniformity of Dosage units	Low	Low	Low	Low	High	Low
Dissolution	Low	Low	Low	Low	High	High
Degradation Products	Low	Low	Low	Low	Low	Low

Table 4.53: Justification for the Initial risk assessment of the manufacturing process

Process Variables	Drug Product CQAs	Justification
Dry Mixing	Assay	Based on the Prior experience of the product development for other markets, the dry mixing time will be kept fix as optimized earlier. So risk is low.
	Uniformity of Dosage units	
	Dissolution	Dry mixing does not have any impact on the Dissolution. So the risk is low.
	Degradation Products	Dry mixing does not have any impact on the Related Substance. So the risk is low.
Granulation	Assay	Granulation process used is base on the prior development work. So the risk is low.
	Uniformity of Dosage units	
	Dissolution	
	Degradation Products	
Drying	Assay	As per the force degradation study data, API is heat stable thus drying is unlikely to impact Assay and Drying time will be kept as per prior development work. The risk is low.
	Uniformity of Dosage units	Uniformity of Dosage units is depends on the earlier manufacturing step like dry mixing and granulation. So the risk is low.
	Dissolution	Drying step will not impact the dissolution of API. The risk is low.
	Degradation Products	As per the force degradation study data, API is heat stable thus drying is unlikely to impact degradation products and Drying time will be kept as per prior development work. The risk is low.
Milling	Assay	The mill screen type & speed may impact the granule size distribution, and flowability. A distribution may affect flow, causing variable tablet weight and assay during compression and also impact on the dissolution. A mesh screen type and speed is selected based on the prior experience of the Product development. So the risk is low. If the mill screen type is changed, risk will need to be reassessed.
	Uniformity of Dosage units	
	Dissolution	
	Degradation Products	Although the screen may heat up during the milling process but as per the force degradation study data, API is heat stable thus milling is unlikely to impact degradation products. The risk is low.

Process Variables	Drug Product CQAs	Justification
Blending & Lubrication	Assay	Blending time can directly impact assay and blend uniformity which can finally impact Uniformity of Dosage Units. However it has no impact on dissolution &degradation products. So risk is low.
	Uniformity of Dosage units	
	Dissolution	
	Degradation Products	
Compression	Assay	Compression process variables can cause tablet weight variability which could cause tablets to fall out-of-specification for assay and uniformity of dosage units. However good flowability was observed for powder blend during the development work. So the risk is low.
	Uniformity of Dosage units	
	Dissolution	Tablets hardness is impacted if compression force varies. The risk is high.
	Degradation Products	DM01 is not susceptible to heat. So the compression is unlikely to impact the degradation product. So the risk is low.
Coating	Assay	The film coating is to be applied to match the trade dress with RLD. Tablet film coating process is unlikely to impact as this attributes have been controlled during the earlier core tablet manufacturing. The risk is low.
	Uniformity of dosage units	
	Dissolution	
	Degradation products	DM01 is heat stable as shown in the force degradation study. Further as API is sensitive to water hydrolysis, Non aqueous film coating is selected. Thus Film coating is unlikely to impact the degradation products.

To address the manufacturing variable which was identified as high risk, following studies were conducted by identification and control of critical process parameters.

• An investigation of Blending & lubrication time

• An investigation of tabletting parameters

Blending and Lubrication Process Development

Identification of Blending Process Parameters and Initial Risk Assessment

The initial risk assessment of the overall manufacturing process presented in Table 61 identified the risk of the blending and lubrication step to impact tablet assay & uniformity of Dosage units as high. Subsequently, blend uniformity was identified as an intermediate CQA of the powder blend from blending and lubrication step.

Process variables that could potentially impact blend uniformity were identified and their associated risk was evaluated. The following table presents the initial risk assessment for the blending and lubrication step.

Table 4.54: Initial risk assessment of the Blending and Lubrication Process variables

Process Step:	Blending and Lubrication	
Output variable: Blend uniformity & Assay		
Variables	Risk Assessment	Justification and Initial Strategy
Blending Variables		
Blender Type	Low	Blender is selected based on the equipment availability and prior experience with the same product.
Rotational Speed	Low	Rotational speed is fixed by equipment constraints. Rotational speed for Blender is fixed at 24 rpm.
Blending Time and Lubrication Time	Medium	Blending & Lubrication time needs to be investigated.

The batches of DM01 tablet 40 mg were prepared with the optimized formula. The manufacturing process of the DM01 tablets were carried out as described in batch no

G4001 for 40 mg . The blending time was kept fixed i.e 10 mins. In order to optimize the final blending (Lubrication) the Relative Standard Deviation (RSD) of the Blend Uniformity of 10 samples during the lubrication was taken as a function of final blending time. Samples were collected at each 3 min, 5 min & 7 minutes and evaluated for the assay and blend uniformity. The results of the same are represented in the below table.

Table 4.55: Blend Uniformity of DM01 Tablets 40 mg

Batch No: G4029 (Batch Size: 2000 Tablets)						
Blending Time	**Blend Uniformity**					
	S1	**S2**	**S3**	**S4**	**S5**	**S6**
3 min	100.3	100.5	99.5	100.0	99.6	99.3
5 min	99.5	98.9	100.1	99.2	100.3	100.0
7 min	99.2	100.4	99.3	99.5	99.8	99.4

Batch No: G4029 (Batch Size:2000 Tablets)							
Blending Time	**Blend Uniformity**				**Mean**	**Assay**	**% RSD**
	S7	**S8**	**S9**	**S10**			
3 min	100.2	102.6	100.5	99.5	100.2	97.3	0.95%
5 min	98.3	99.7	98.7	99.5	99.4	101.8	0.65%
7 min	99.6	100.4	99.5	100.3	99.7	100.4	0.46%

Conclusion:

For 40 mg, adequate BU results were obtained for the final blending process. RS values for time interval studied were found less than 2 % for, which is within the acceptance criteria i.e. RSD < 5%. Hence lubrication time 5 minutes was finalized.

Tablet Compression Process Development

Based on the initial risk assessment of the overall manufacturing process shown in Table 61, the risk of the compression step to impact dissolution of the tablets was identified as high. Tablet hardness was identified as a variable that could potentially impact the dissolution. Tablets were compressed at different hardness and the evaluated for the dissolution. Data are summarized in the following tables.

Table 4.56: Physical Parameters of the DM01 Tablet 40 mg

Observation				
Sr. No	**Parameter**	**40 mg**		
	Batch No	**G4013**		
		Low Hardness	**Optimum Hardness**	**High Hardness**
1.	Average weight	420.0 mg	420.0 mg	420.0 mg
2.	Punch Size	15 X 7 mm oval sub concave	15 X 7 mm oval sub concave	15 X 7 mm oval sub concave
3.	Thickness	5.40-5.50 mm	5.15-5.25 mm	4.95-5.10 mm
4.	Disintegration Time	1 min-1 min 30 sec	4 min 30 sec to 5 min 30 sec	6 min 30 sec-7 min
5.	Resistance to crushing	76-91 N	123– 143 N	150-186 N
6.	Friability	Nil	Nil	Nil

Table 4.57: Dissolution profile of DM01 Tablet 40 mg

DM01 Tablets 40 mg Batch No: ASOMDTG4013			
	Low Hardness	**Optimum Hardness**	**High Hardness**
Batch. No	**G0058**	**G0060**	**G0059**
Time			
5	47	57	51
10	66	73	72
15	75	80	80
20	79	84	84
30	85	88	89
45	88	90	91
60	90	91	92

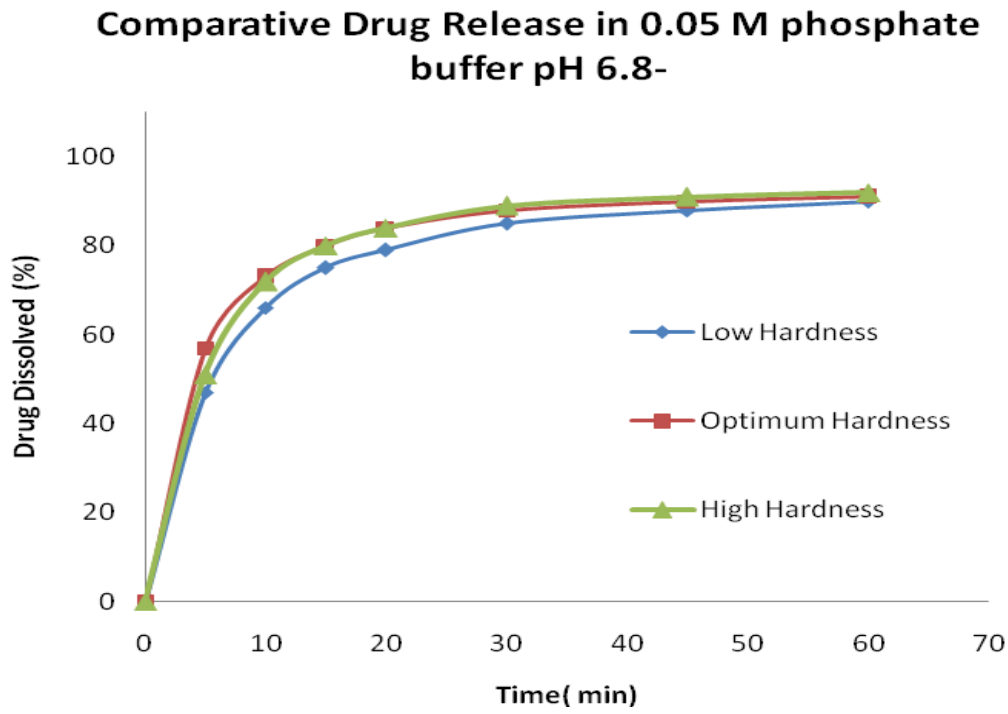


Figure 4.9: Comparative Drug Release profile of DM01 Tablet 40 mg (Effect of Hardness)

Conclusion:

Based on data it was observed hardness does not have much impact on release profile of the tablet.

Updated Risk assessment of the manufacturing process for DM01 Tablet 40 mg.

During process development, the identified high risks for each process step were addressed. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment was updated. Following table provides the updated risk assessment of the manufacturing process for DM01 Tablets 40 mg.

Table 4.58: Updated risk assessment of the manufacturing process for DM01 Tablet 40 mg

Initial risk assessment of the manufacturing process for DM01 Tablet 40 mg						
Drug Product CQAs	**Dry mixing**	**Granulation**	**Drying**	**Milling**	**Blending & Lubrication**	**Compression**
Assay	Low	Low	Low	Low	Low*	Low
Uniformity of Dosage units	Low	Low	Low	Low	Low*	Low
Dissolution	Low	Low	Low	Low	Low	Low*
Degradation Products	Low	Low	Low	Low	Low	Low

***:** The level of the risk reduced from the initial risk assessment.

Following table provides the justification for the reduced risk following process development.

Table 4.59: Justification for the updated risk assessment of the manufacturing process

Process Step	Drug Product CQAs	Justification
Blending & Lubrication	Assay	The selected Number of revolution for Blending and Lubrication, acceptable assay, blend uniformity and dissolution were achieved. So the risk is reduced from high to low..
	Uniformity of Dosage units	
Compression	Dissolution	For this Unit operation, at the set parameter of tablet compression effect of Hardness on dissolution were demonstrated. Within the range studied for hardness, more than 75 % dissolution at 45 min was achieved for all strength. Hence the risk is reduced from high to low.

4.4.5.6 Stability data of DM01 tablets 40 mg

Table 4.60: Stability Data of DM01 Tablets 40 mg

Test Name	Specification	Initial	2 Months 40°C/75%	2 Months 25°C/60%
Batch No.		**GR5002**	**G5002**	**G5002**
Description	White, round, biconvex, film coated tablets			
Average Weight	430.4 mg ± 3%	433.4 mg	431.5 mg	432.2 mg
Loss on Drying	NMT 6.0% w/w	2.43%	3.35%	3.80%
Dissolution Profile	NLT 85%(Q) in 45 min	87%	86%	86.5%
Related substances				
Imp A	NMT 1.0%	0.23%	0.53%	0.34%
Single max unknown	NMT 0.2%	0.025%	0.05%	0.02%
Total impurities	NMT 2.0%	0.296%	0.62%	0.39%
%Assay	90.0 % to 100.0 % of label claim	97.10%	98.50%	97.50%

Final formula

Proposed formula for DM01 Tablets 40 mg was mentioned in below table.

Table 4.61: Final proposed formula of DM01 Tablets 40 mg

Sr No	**Strength**	**40 mg**
	Ingredients	**Qty/Tablet (mg)**
Dry Mixing		
1.	DM01	40.00
2.	Lactose monohydrate	250.44
3.	Hydroxypropyl cellulose (Klucel EXF)	15.83
4.	Low substituted Hydroxypropyl cellulose (LH-21)	20.00
5.	Microcrystalline cellulose (Avicel pH 101)	35.00
Granulation		
6.	Isopropyl alcohol	q.s.
Lubrication		
7.	Microcrystalline cellulose (Avicel pH 102)	40.00
8.	Low substituted Hydroxypropyl cellulose (LH-21)	14.53
9.	Magnesium stearate	4.20
	Theoretical weight of Core tablet	420.00
Coating		
10.	HPMC 6 cps	6.20
11.	Talc	2.10
12.	Titanium dioxide	2.10
13.	Ferric oxide yellow	-
14.	Dichloromethane	Q.S.
15.	Isopropyl alcohol	Q.S.
	Theoretical weight of Coated tablet	**430.40**

4.5 Control Strategy

The control strategy for the manufacture of DM01 40 mg, is proposed and presented in following table. The control strategy includes API and excipient material attributes to be controlled, in-process controls, high risk process parameter and the proposed operating ranges.

Table 4.62: Control Strategy for DM01 Tablets 40 mg

Attributes or Parameter	Ranges	Type of Control
Blending		
DM01 particle size distribution d 0.9	Should be less than 10 µm.	Drug substance specification
Blending and Lubrication Speed	24 RPM ± 1RPM	Operating Range
Blending and Lubrication Time	10 min blending followed by 5 min Lubrication	PAR
Blend Uniformity	BU < 5 % RSD	In-process control
Blend Assay	95-105 % w/w	In-process control

Table 4.63: Control Strategy for DM01 Tablets 40 mg

Tablet Compression In Process Controls		
Parameter	**Ranges**	**Type of Control**
Compression Force	To be recorded	Operating Range of Machine
Press Speed	15-50 RPM	Operating Range of Machine
Average wt of tablet	420.0 mg ± 3 %	In-process control
Uniformity of wt.	420.0 mg ± 5% w/w	In-process control
Hardness	80 -180 N (Target 130 N)	In-process control
Disintegration time	Within 5-7 min	In-process control

Control Strategy for Raw Material Attributes

The drug substance particle size distribution limits arise from a combination of its impact on dissolution which may affect *in vivo* performance. During formulation development, a particle size distribution with a $d_{0.9}$ value less than 10 µm was found to ensure good uniformity of dosage units using a wet granulation approach and a fixed blending process. Finally products CQA's to be achieved using a drug substance $d_{0.9}$ value less than 10 µm.

Control Strategy for Blending and Lubrication

The updated risk assessment for the blending and lubrication process step demonstrates that the identified risks to assay and blend uniformity have been reduced by adjusting the number of revolutions. Blending time of 10 min and lubrication time of 5 min was fixed to achieve sufficient blend uniformity.

Control Strategy Tablet Compression

The control strategy for compression is to maintain the in-process tablet attributes of weight, hardness, thickness, friability and disintegration within the required ranges. The fill cam below the die table adjusts the lower punch to the appropriate height to control fill depth and ultimately tablet weight. The target compression force required to produce tablets with the desired hardness, and ultimately friability and disintegration, is established at the beginning of each run. After the initial set up of the compression machine parameters In process parameters are to be monitored and recorded at fixed interval.

5. Summary & Conclusions

- The following experimental work deals with the development of DM01 Tablet 40 mg. DM01 is indicated for the treatment of hypertension. Quality by Design (QbD) approach was used to develop DM01 tablet .Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD product, and consideration of the RLD label.
- Identification of critical quality attributes (CQA's) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the drug product. Investigation during pharmaceutical development focused on those CQA's that could be impacted by a realistic change to the drug product formulation or manufacturing process.
- Risk assessment was used throughout development to identify potentially high risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated after development to capture the reduced level of risk based on improved product and process understanding.
- Excipients were identified in line to that of reference product and based on the literature search. Two strategies were tried namely direct compression and wet granulation by RMG (rapid mixture granulator).Wet Granulation method was selected based on the drug substance characteristics and release profile to achieve desired QTPP.
- As a part of QbD approach, Design of Experiments (DoE) using Box-behnken study was conducted in formulation development and impact of change of critical formulation factors on dissolution and disintegration. The formulation composition was finalized based on the knowledge gained from the DoE study. Alongwith formulation factors, certain critical process optimization studies were conducted to established consistency of process within targeted ranges.
- Finally, a control strategy was arrived that includes the material attributes and process parameters identified as potentially high risk variables during the initial risk assessment. Control strategy also includes in-process controls and finished product specifications.

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