"DESIGN & OPTIMIZATION OF FLUIDIZED HOT MELT GRANULATION TECHNIQUE FOR DEVELOPMENT OF MODIFIED RELEASE TABLETS"

A Thesis Submitted to

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in Partial Fulfillment for the Award of the Degree of

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IN

PHARMACEUTICAL TECHNOLOGY &

BIOPHARMACEUTICS

BY

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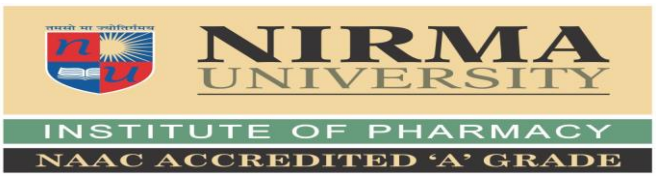

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MAY 2017

CERTIFICATE

This is to certify that the dissertation work entitled "Design & Optimization of Fluidized Hot Melt Granulation Technique for Development of Modified Release Tablets" submitted by Ms. Dolly Jetha with Regn. No. 15MPH105 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 Piramal Enterprises Limited, Pharmaceutical Development Services 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.

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DECLARATION

I hereby declare that the dissertation entitled "Design & Optimization of Fluidized Hot Melt Granulation Technique for Development of Modified Release Tablets", is based on the original work carried out by me under the guidance of Mr. Tejas Shah, Sr. Principal Scientist, Piramal Enterprises Limited, Pharmaceutical Development Services, Ahmedabad and Prof. Tejal Mehta, Professor and HOD, 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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Real life isn't always going to be perfect or go the way we want it to, but a recurring acknowledgement of what is working in our life can help us not only survive but surmount the difficulties.

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List of Abbreviations

FHMG	fluidized hot melt granulation
MR	modified release
API	active pharmaceutical ingredients
DMF	drug master file
OVAT	one variable (factor) at a time
Kg	kilogram
mg	milligram
Kp	kilopascal
mm	millimeter
min	minutes
hr	hour
CFM	cubic flow per minute
SD	standard deviation
RSD	relative standard deviation
°C	degree centigrade
RH	relative humidity
LOD	loss on drying
PSD	particle size distribution
#	mesh
CU	Content uniformity
v/s	verses
BCS	biopharmaceutical classification system
g/mol	gram per mole
ppm	Parts per million
QbD	quality by design
QTPPs	quality target product profile
CQAs	critical quality attributes
CMAs	critical material attributes
CPAs	critical process attributes
DoE	design of experiment
ml	milliliter
µg/ml	microgram per milliliter
λ_{max}	wavelength for maximum absorption
nm	nanometer

rpm	rotations per minutes
UV	ultra-violet spectrophotometer
FTIR	fourier transform infrared Spectrophotometer
DSC	differential scanning calorimetry
NMT	not more than
ANOVA	analysis of variance
F1	dissimilarity value for dissolution study
F2	similarity value for dissolution study

The most preferred and predominant route for drug delivery is oral route as it provides us with suitability of administration, high patient compliance and one of the most suitable way to deliver drug for systemic effect. Modified release (MR) dosage forms are the ones in which the pattern of drug release is deliberately altered from that of a conventional dosage formulation (Immediate Release) inorder to reach the desired therapeutic objective or for better patient compliance. While formulating a MR formulation, the most essential factors for the effect and efficient therapeutic performance is the sustained concentration of the drug in body through sustained drug release from the formulation.

The model drug has an anti-anginal effect. Thus, the main effect of the drug is desired in the early morning hours as the angina attacks mostly occur in the morning due to circadian rhythm. The drug shows high solubility and high permeability hence considered as BCS class I drug. The half-life of drug is 3.0 - 4.5 hours. The bioavailability of the drug is approx. 40% due to the first pass metabolism. The drug demonstrates poor compressibility and poor flow.

Hence, the objective was to prepare a MR formulation which controls the release of this highly soluble and gives a peak plasma concentration of the drug in the body in early morning hours when a patient consumes the formulation before going to bed. The release wass modified by preparation of a hydrophobic matrix tablet using fluidized hot melt granulation technique. This technique not only control the release of this highly soluble drug but also produces granules with good – excellent flow properties.
Thus, the aim and objective of the project were as following:

Aim

To explore Fluidized Hot Melt Granulation as a **platform technology** for preparing modified release tablets of BCS class I drug**.**

Objectives

- Drug substance characterization.
- RLD characterization and identification of CQAs and risk assessment related CMA, various manufacturing parameters are evaluated and selection was done on the bases on experimental data obtained..

- Pre-formulation studies for excipient selection.
- To prepare MR tablets for a BCS class I Model Drug X with matching performance to the commercial MR tablets.
- Physicochemical Characterization including, Friability, Hardness, Content uniformity, Drug Release (In vitro) etc. of optimized formulation.
- Comparison of Optimized formulation with a Reference product.
- To study the viability of Hot melt granulation as an alternative for Hot melt extrusion for the preparation of modified release tablets.
- To screen critical process parameters of Fluidized Hot Melt Granulation (FHMG) technique using Quality by Design approach.
- Generation of Design Space.
- To perform stability studies as per ICH guidelines.

1.1 Introduction to Modified Release Dosage Forms[1,2]

Modified release (MR) dosage forms are the ones in which the pattern of drug release is deliberately altered from that of a conventional dosage formulation (Immediate Release) inorder to reach the desired therapeutic objective or for better patient compliance. MR drug products can be of, but are not restricted to, the following types: delayed release (eg, enteric coated), extended release (ER), and orally disintegrating tablets (ODT).

1.2 Need for Granulation

Orally administered drug deliver platforms, such as tablets and capsules, are considered as the preferred and most patient – convenient dosage forms available today and trusted since centuries. This is primarily because of their advantages like ease of administration, convenience of handling and higher stability when compared to their liquid counterparts. Oral solid dosage forms are typically an intricate blend of excipients (diluents, binders, disintegrants, glidants, lubricants and flavors) and APIs.[3]

Table 1.1 Comparison of Powder and Granules properties

Powder	Granules
	
Comparatively poor flow properties	Good flow as compared to powders. Better choice for compression of tablets
More likely to harden / cake formation on long storage	Less likely to cake formation.
Reactively poor compressibility	Good compressibility

Powder	Granules
Chance of non-uniformity is higher drug may not be uniformly distributed due to the cohesive nature of powders	Relatively more conformity of content in case of granules
Comparatively less appealing	Have a more elegant appearance
More dust due to small particle size	Generate less dust on handling
Relatively simple method of processing/formulation	It involves more processing, exposure to heat and contact with solvents

Table 1.1 shows a comparison between powders and granules properties. It is clear from the table that the handling of the granules is more easier and they there possess many advantages over powders. Thus, granulation of powder forms an important unit operation in the pharmaceutical industry

An adequate mixing and/or granulation of these excipients and APIs is of prior importance to successfully manufacture acceptable pharmaceutical products. The main aim of powder granulation is to produce free-flowing and non-segregating blend, which may be reproducibly metered in subsequent processes after granulation. Thus, the study of the granule behavior is important.[4] This ensures that the resulting agglomerates possess the required flowability, compressibility, and avoids powder demixing during post-granulation processes. The granulation process is expected to inculcate the desired granule properties to the powder blend within some prescribed range and these granule attributes depend on the application in hand. Size distribution of the agglomerates also affects the flow, segregation properties, and compaction behavior. Granule voidage not only controls strength and impacts tablet dissolution behavior, but also the blend compaction behavior and subsequently the tablet hardness.

Objective of granulation include, but are not limited to, the following[3]:

- Production of a useful structure form.
- Reduced propensity to caking.
- Creation of non-segregating blends of powder ingredients.
- Control of solubility.
- Control of porosity, harness, surface-to-volume ratio and particle size.

1.3 Array of available Granulation techniques & their manufacturing challenges

Conventional technique for granulation of pharmaceutical powder involves dry or wet methods. Hot Melt Extrusion has also been recently demonstrated as a viable technique for granulation of powders and to prepare several dosage forms[5,6].

Direct Compression[7]

Inspite of the benefits of direct compression technique like reducing process time and avoiding wetting and drying steps, they carry inherent processing difficulties including:

1. Its inability to compress powder and API that are crystalline in nature.
2. Problems associated with powders having erratic flow properties like weight variation and hardness variation.
3. Powder segregation which leading to product non-uniformity.
4. Need for specialized excipient with directly compressible property. This increases the cost

Due to these limitations, wet granulation is a more preferred and widely accepted for powder granulation technique.

Roller Compaction[8,9]

One of the major disadvantages of roller compaction is a phenomenon called ‘loss of reworkability’. Over compaction can result in discolored, extremely hot, severely cracked or plasticized ribbons. A splitting of ribbons can also be observed.

Tablets made by this technique often show inferior tensile strength compared to tablets prepared by wet granulation.

Because no liquid binder is used, high amounts of fines of un-compacted material and less product yield is obtained due to sticking to the rollers when compared to other granulation techniques.

A proper balancing of parameters including roll pressure, roll speed and feeding rate of starting material is needed since these parameters determine the product properties (e.g. ribbons, granules)

Non-homogeneity of the ribbons can also be observed for blend with poor flow due to segregation

Slugging

Slugging not only carrier the demerits of the roller compactor, but also the following disadvantages:

1. Low manufacturing throughput per hour.
2. More energy and time required to produce 1 Kg of slugs than 1 Kg of roller compact.

Wet granulation[9]

A multiple unit operations technique including a granulation followed by a drying stage. This makes wet granulation for time consuming process since aqueous based wet granulation involves longer time periods for drying. Also, aqueous wet granulation is an unsuitable method for agglomeration of powders with a moisture sensitive API or excipient. Due to this, moisture sensitive drugs are granulation using organic solvents. The problem associated while working with organic solvents is the residual solvent limits. Complete removal of the solvents from the product is important for patient safety. The major issue with wet granulation technique is the end point determination. An inaccurate end point may either lead to excess binder addition (leading to wet mass formation) or insufficient binder adding (leading to nonreproducible particle size distribution since more fines are produced and desired characteristics of the granule are not obtained). Thus, wet granulation requires skills to determine the end point since a small change in the amount of binder can highly impact the end product character. **Fig. 1.1** summarizes the disadvantages of the wet and dry granulation methods;

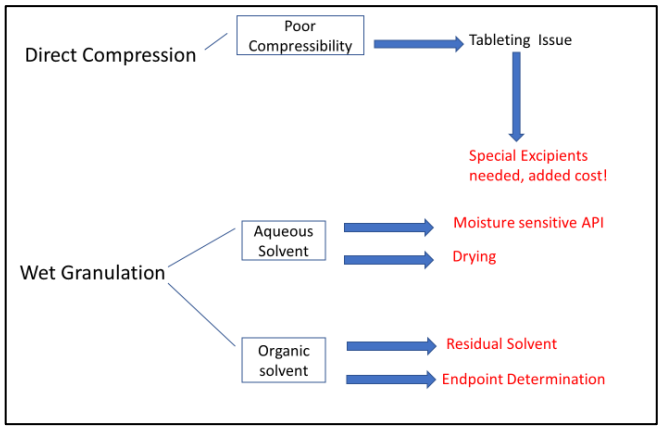


Fig. 1.1 Disadvantage of Dry and Wet methods for Granulation

Hot Melt Extrusion (HME)

The common failure or defects which are normally occurring in extrusion process are due to three main causes: mould design, material selection, and inappropriate processing parameters.[10,11] In many cases, the failures occur during the processing and these failures causes some defects that can be found in extruded parts such as: rough surface, extruder surging, thickness variation to name a few[12]. **Table 1.2** shows the various Processing Problems and their impact on the product and **Fig.1.2** shows various process problems associated hot melt extrusion;

Table 1.2 HME Processing Problems and their Impact on the product[10,12]

Processing Problems	Impact
Powder with poor flow	1. Product Variation 2. Solid bridging at the throat of hopper
Surging	1. Variation in the thickness of the product 2. Air entrapment
Poor mixing	1. Non-uniformity of Extrudes 2. Solid polymer blocking the channel
Feed rate variation	Melt toughness or fracture. This refers to fine ridges or rough surface seen when the melt comes too fast out of a narrow die.
Overheating / localized heating	Product degradation

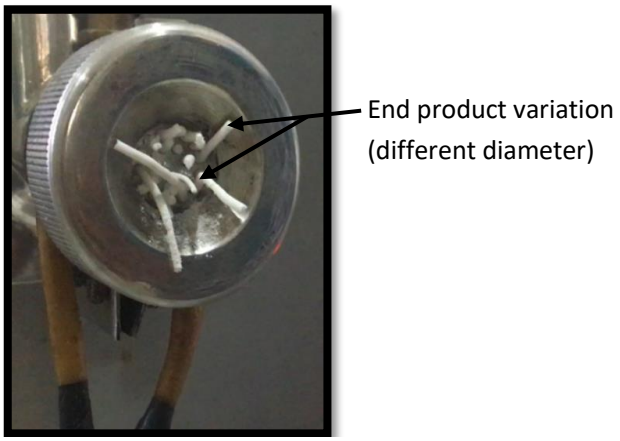


Fig. 1.2(a): Surging Phenomenon - Variation in the thickness of the product through extrusion screen

Fig. 1.2(b): Solid polymer blocking the channel in the HME screw

Thus, there is a growing need for an alternative process to combat the negatives of the conventional technique and for dramatically improving particle processing so as to ensure reproducible results.

1.4 Fluidized Hot Melt Granulation: A new approach

An emerging alternative to combat the drawbacks of traditional granulation techniques is the Fluidized Hot Melt Granulation (FHMG). Here, granulation is conducted at elevated temperature to alter/modify the physical nature of one or more components (known as the meltable binder), so as to agglomerate fluidized dry powders in controlled conditions[13].

The idea of using molten binding liquid for granulation as an alternative to conventional aqueous or organic binding liquids started in late 1970s. However, the concept gained interest a decade later after the use of high-shear mixer and fluidized granulators for melt granulation came into picture[14,15]. High-shear mixer gained grater popularity for use in melt granulation, and was widely known as the **single pot process**[16].

Melt granulation involves adding the binder either in the form of molten liquid on the fine solid particles bed or in the form of solid which melts inside the system during the process. Generally, the amount of binder used is 10-30% w/w with respect to that of fine solid particles. The melting temperature of the binder can be attained either by application of heat external (heat jacketing) or heat can be generated from inter-particulate friction during high speed mixing in the rapid granulating equipment. A meltable binder having melting point in range of 50°-100°C is suitable for melt granulation. A meltable binder with a melting point lower than 50°C are generally unsuitable as the end products as they may be liable to melting, softening or sticking during handling and storage. On the other hand, binders of high melting temperatures are not desirable due to greater risk of thermal instability to the drugs used when very high heat is required for the melting of binders[13].

The basic principle in melt granulation processes are fairly similar to those of the wet (aqueous or organic) granulation process expect that the binders of melt granulation are not evaporated. Unlike the conventional use of aqueous or organic solvents as binder, the binding liquid in melt process remains as a constituent of the formulation[17].

The melting point of the excipients used should be atleast 20°C higher than the maximum processing temperature. This prevents degradation of the excipients and also avoids excessive softening of the solid. It is important to avoid softening of the excipients (fillers and APIs) as they form the support for the molten binding liquid during the nucleation process and subsequent building-up stage of agglomerate structure[18].

The meltable binder can be categorized as hydrophobic or hydrophilic depending on their chemical nature. **Table 1.3(a) & 1.3(b)** shows the list of binders that can be sued for FHMG process. With an appropriate selection of meltable binder, both immediate and prolonged release agglomerates can be prepared in single step using processor approach[19,20,21].

Hydrophobic	
Name	Melting Point (°C)
Carnuba wax	82-86
Parafin wax	68-69
Hydrogenated Castor oil	83-87
Hydrogenated soyabean oil	61-63
Beeswax	62-64
Compritol 888 ATO	69-74
Stearic Acid	69-70
Stearlyalcohol	50-51
Gelucire 50/13	50-53

1.3(a): Hydrophobic Binder for FHMG

Hydrophilic	
Name	Melting Point (°C)
PEGs	
PEG 6000	55-63
PEG 8000	60-63
PEG 20000	60-63
Poloxamers	
188	52-57
338	57
407	52-57

1.3(b): Hydrophilic Binder for FHMG

Table 1.3 Array of Meltable binders for FHMG

The newer approaches of FHMG including the *in-situ* melt granulation pose advantages like narrow granules particle size distribution, good flow properties of granules and higher compressibility. This technique is found comparable to the currently available spray on melt granulation technique[22,23].

FHMG is a rapid technique which does not require the dry powder blends to have high level of fluidity or compressibility, and replicates the simplicity of dry techniques as it can be performed in a single step. This is its advantage over wet techniques which require

transfer from the granulator to the drying equipment, and this commonly leads to process loss, contamination, increased processing time and increased dust levels which are of particular importance when dealing with potent drugs[24].

1.5 FHMG v/s HME

FHMG eludes the use of solvent, thus negating the problems associated with wet granulation like in-process hydrolysis and solvent removal[17]. FHMG carries with it the advantages of the Hot Melt Extrusion (HME) like absence of solvents, few processing steps, suitable process for granulation of moisture sensitive drugs and improved bioavailability[19], and is a potent alternative to HME due to the reduced equipment cost, higher equipment simplicity, more controlled working temperature and absence of prior mixing stage. The mechanical shear in HME due to the screw movements may cause polymer scissoring and depolymerization. This is not observed in FHMG since it is a fluidization process. Moreover, FHMG can be used for granulating powders with poor flow properties, which is a limitation in HME technique[10,12].

1.6 Model Drug X[25]

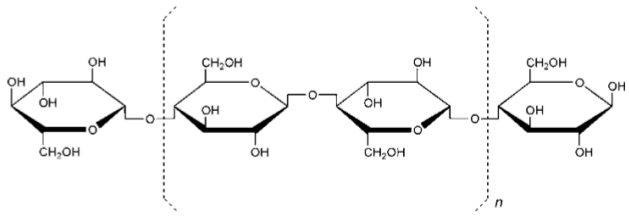
Table 1.4 Introduction to Drug X

Therapeutic Category	Calcium Channel Blocker
BSC class	I
Molecular Weight	450.98 g/mole
Polymorphism	No reported polymorphs
Solubility	Freely soluble: Chloroform, Formic acid, Methanol, Water Sparingly Soluble: Dehydrated Alcohol Practically Insoluble: Benzene Insoluble: Ether
Melting Point	212 – 213°C with decomposition
Log P	2.73 (Ref: Drug Bank, ChemAxon)
pKa	Strong Acid: 12.86 Strong Base: 8.18 (Ref: Drug Bank)
Indication	Treatment of angina pectoris and hypertension
Dose	60 mg
Pharmacokinetics	
Absorption	Rapidly absorbed after oral administration
Elimination route	Extensively metabolized, predominately due to hepatic metabolism
T_{max}	~ 3 hours
Half Life	3.0 – 4.5 hours (Ref: Drug Bank)
Protein Binding	70 – 80% (Ref: Drug Bank)
Bioavailability	~ 40% (Well absorbed 90% but less bioavailability due to first pass effect)

1.7 Excipients[26]

Microcrystalline Cellulose (MCC)

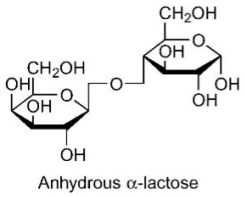
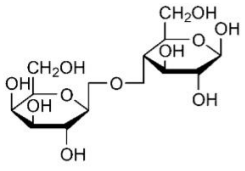
Table 1.5 Introduction to Microcrystalline Cellulose

Sr No.	Property	Description
1.	Non-propriety names	BP: Microcrystalline cellulose JP: Microcrystalline cellulose PhEur: Cellulosum microcristallinum USPNF: Microcrystalline cellulose
2.	Structural Formula	
3.	Functional category	Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.
4.	Application in P'ceutical industry	MCC is primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. MCC also has some lubricant and disintegrant properties that make it useful in tableting.
5.	Description	MCC is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.
6.	Powder Properties	**Angle of repose**: 34.4° **Density (bulk):** 0.28 – 0.33 g/cc; **Density (tapped)**: 0.478g/cm^3; **Density (true)**: 1.512–1.668g/cm^3 **Flowability**: 1.41g/s **Melting point**: chars at 260–270°C.

Sr No.	Property	Description
		Moisture content: Less than 5% w/w. However, different grades may contain varying amounts of water.
7.	Stability and Storage condition	It is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.
8.	Regulatory Status	GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive IIG, nonparenteral medicines licensed in the UK and in the Canadian List of Acceptable Non-medicinal Ingredients.

Lactose Monohydrate

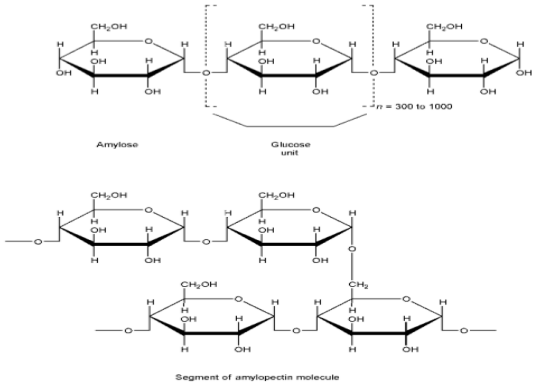
Table 1.6 Introduction to Lactose Monohydrate

Sr No.	Property	Description
1.	Non-propriety names	BP: Lactose monohydrate PhEur: Lactosum monohydricum JP: Lactose USPNF: Lactose monohydrat
2.	Structural Formula	 Anhydrous α-lactose  Anhydrous β-lactose
3.	Functional category	Binding agent, diluent for dry-powder inhalers, tablet binder, tablet and capsule diluent.

Sr No.	Property	Description
4.	Application in P'ceutical industry	Lactose is used as a filler or diluent in tablets and capsules, dry-powder inhalation and to a more limited extent in lyophilized products and infant formulas. Fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate, containing small amounts of anhydrous lactose.
5.	Description	Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting.
6.	Powder Properties	**Angle of repose**: 32.8° for Tablettose. **Density (true):** 1.545g/cm^3 Density (bulk). **Melting point**: 201–202°C (dehydrated) **Moisture content**: 5% w/w water of crystallization and normally has a range of 4.5–5.5% w/w water content
7.	Stability and Storage condition	Mold growth may occur under humid conditions (80%relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Lactose should be stored in a well-closed container in a cool, dry place.
8.	Regulatory Status	Included in the FDA IIG, nonparenteral and parenteral medicines licensed in the UK and in the Canadian List of Acceptable Non-medicinal Ingredients.

Pregelatinized Starch

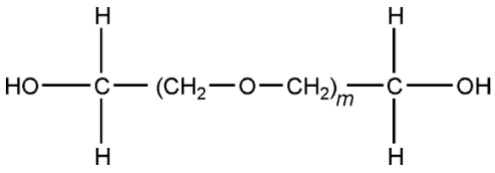
Table 1.7 Introduction to Pregelatinized Starch

Sr No.	Property	Description
1.	Non-propriety names	BP: Pregelatinised starch PhEur: Amylum pregelificatum USPNF: Pregelatinized starch
2.	Structural Formula	
3.	Functional category	Tablet and capsule diluent, disintegrant; tablet binder.
4.	Application in P'ceutical industry	Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant. It may be used as a tablet binder in dry-compression or direct compression processes. In such processes, pregelatinized starch is self-lubricating. Pregelatinized starch may also be used in wet granulation processes
5.	Description	Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has as light characteristic taste.
6.	Powder Properties	**Angle of repose**: 40.7° **Density (bulk)**: 0.586g/cm^3 **Density (tapped)**: 0.879g/cm^3 **Density (true)**: 1.516g/cm^3

Sr No.	Property	Description
		Flowability: 18–23% (Carr compressibility index) **Moisture content**: pregelatinized maize starch is hygroscopic. **Particle size distribution**: 30–150mm, median diameter 52mm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149mm); and less than 0.5% retained on a US #40 mesh (420mm). **Solubility**: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization.
7.	Stability and Storage condition	Pregelatinized starch is stable but hygroscopic material, so it should be stored in a well-closed container in a cool, dry place.
8.	Regulatory Status	Included in the FDA Inactive Ingredients Guide (IIG) and non-parenteral medicines licensed in the UK.

Polyethylene glycol 6000

Table 1.8 Introduction to Polyethylene glycol 6000

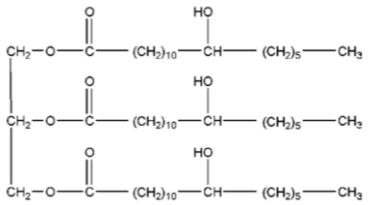
Sr No.	Property	Description
1.	Non-propriety names	BP, BP, PhEur: Macrogols USPNF: Polyethylene glycol
2.	Structural Formula	
3.	Functional category	Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.
4.	Application in P'ceutical industry	In solid-dosage formulations, higher-molecular-weight PEGs can enhance the effectiveness of tablet binders and impart plasticity to granules.

Sr No.	Property	Description
		PEGs can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. PEGs grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents.
5.	Description	Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.
6.	Powder Properties	**Density**: 1.15–1.21g/cm^3 at 25°C for solid PEGs. **Melting point**: 50–58°C for PEG 4000; 55–63°C for PEG 6000; 60–63°C for PEG 8000; 60–63°C for PEG 20000. **Moisture content**: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g. PEG 4000 and above, are not hygroscopic. **Solubility**: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are

Sr No.	Property	Description
		slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.
7.	Stability and Storage condition	PEGs should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.
8.	Regulatory Status	Included in the FDA IIG, non-parenteral and parenteral medicines licensed in the UK and in the Canadian List of Acceptable Non-Medicinal Ingredients.

Hydrogenated Castor Oil

Table 1.9 Introduction to Hydrogenated Castor Oil

Sr No.	Property	Description
1.	Non-propriety names	BP: Hydrogenated castor oil PhEur: Ricini oleum hydrogenatum USPNF: Hydrogenated castor oil
2.	Structural Formula	
3.	Functional category	Extended release agent, stiffening agent, tablet and capsule lubricant.
4.	Application in P'ceutical industry	Hydrogenated castor oil is a hard wax with a high melting point used in oral and topical pharmaceutical formulations. In topical formulations, it is used to provide stiffness to creams and emulsions. In oral formulations, it is used to prepare sustained release tablet and capsule preparations. It may be used as a coat or to form a solid matrix. Hydrogenated castor oil is additionally used to lubricate the die walls of tablet presses and is similarly used as a lubricant in food processing. It is also used in cosmetics.

Sr No.	Property	Description
5.	Description	It occurs as a fine, almost white or pale yellow powder or flakes.
6.	Powder Properties	**Density**: 0.98–1.10g/cm^3 **Flash point**: 316°C (open cup) **Moisture content**: 40.1% **Particle size distribution**: 97.7% 51000mm in size for flakes. **Solubility**: practically insoluble in water; soluble in acetone, chloroform, and methylene chloride.
7.	Stability and Storage condition	Hydrogenated castor oil is stable at temperatures up to 150°C. Hydrogenated castor oil should be stored in a well-closed container in a cool, dry place.
8.	Regulatory Status	Accepted in the USA as an indirect food additive. Included in the FDA IIG, non-parenteral medicines licensed in the UK and in the Canadian List of Acceptable Non-Medicinal Ingredients.

Glyceryl Behenate[27,28]

Table 1.10 Introduction to Glyceryl Behenate

Sr No.	Property	Description
1.	Non-propriety names	BP, PhEur, Gyceryl dibehenate USPNF: Gyceryl Behenate
2.	Empirical Formula	The PhEur 2005 describes glyceryl dibehenate as a mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols. The USPNF 23 describes glyceryl behenate as a mixture of glycerides of fatty acids, mainly behenic acid. It specifies that the content of 1-monoglycerides should be 12.0–18.0%
3.	Functional category	Coating agent, tablet binder, tablet and capsule lubricant.

Sr No.	Property	Description
4.	Application in P'ceutical industry	Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations. In cosmetics, it is mainly used as a viscosity-increasing agent in emulsions. In pharmaceutical formulations, glyceryl behenate is mainly used as a tablet and capsule lubricant and as a lipidic coating excipient. It has been investigated for the encapsulation of various drugs such as retinoids. It has also been investigated for use in the preparation of sustained release tablets; as a matrix-forming agent for the controlled release of water-soluble drugs; and as a lubricant in oral solid dosage formulations, and it can also be used as a hot-melt coating agent sprayed onto a powder.
5.	Description	Glyceryl behenate occurs as a hard waxy mass or pellet with a faint odor.
6.	Powder Properties	**Melting point**: 65–778C **Solubility**: soluble, when heated, in chloroform and dichloromethane, practically insoluble in ethanol (95%), hexane, mineral oil, and water.
7.	Stability and Storage condition	Glyceryl behenate should be stored in a tight container, at a temperature less than 358C.
8.	Regulatory Status	GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (capsules and tablets). Included in the Canadian List of Acceptable Nonmedicinal Ingredients.

1.8 A brief introduction to Quality by Design (QbD)

QbD is aimed at a greater understanding of the product and its manufacturing process which ensures development of a product with the desired safety and efficacy. QbD not only helps in systematic formulation development but also is helpful in well-organized filing of a product to the FDA[29,30].

QbD needs a good understanding of how a process or formulation variable impacts the target product quality. QbD is an organized approach for formulation development and has the following elements[31]:

• Defining the quality target product profile (**QTPP**). These attributes are related to the product's quality, safety and efficacy,
e.g., the route of administration, dosage form, bioavailability, strength, and stability;

• Identifying potential critical quality attributes (**CQAs**) of the drug product. This is done to gain knowledge of those product characteristics that have an impact on product quality. This knowledge is used study and control the product characteristics so as to achieve a reproducible product with the desired safety and efficacy.

• Determining the critical process attributes (**CPAs**) and critical material attributes (**CMAs**) the drug & excipients to deliver drug product possessing the desired quality.

• Selecting a suitable manufacturing process for product development.

• Development of a **Control Strategy** from the product and product understanding so to ensure process performance and product quality while working within the design space.

The knowledge from available literature and the potential drug product CQAs derived from the QTPP form the basis of the product and process development. The number of CQAs can be altered when the formulation and manufacturing process are selected and as product knowledge and process understanding increase[32].

Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk

management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product[33].

ICH Q9 discusses the role of risk management in pharmaceutical development as follows[33]:

1. To select a suitable product design and process strategy.
2. To improve knowledge of product performance over a wide range of processing options (CPAs), process parameters and material attributes like the particle size distribution, moisture content, flow properties.
3. To assess the CMAs and packaging materials.

Articles

- ## Hot Melt Granulation

Jay P. Lakshman et al[34]

In this article, melt granulation (MG) process is compared with wet granulation (aqueous) (WG) and solvent granulation (SG) to produce a formulation by enhancing tableting properties of a poorly compactible high dose drug. Under identical compression force, the hardness of tablets obtained was MG>SG>WG and friability was found to be MG<SG<WG. Unlike SG and WG, MG was not sensitive to changes in atmospheric moisture levels. MG process can decrease tablet size of high-dose drugs since it reduces the need for addition of relatively large amounts excipients needed to improve the compressibility of the drug.

Viviane Nart et al[35]

This paper was aimed at developing sustained release mini-tablets containing the soluble drugs captopril and metformin hydrochloride with carnauba wax used as a lipid component by melt granulation technique. This method improved the flow and tabletability of captopril and metformin hydrochloride. The effect of carnauba wax as granulating excipient in the preparation of minitablets suggested that the excipient decreased the contact with the aqueous medium of the particles of the drug, reducing its release rate and delaying the disintegration of the dosage form.

- ## Hot Melt Extrusion

M.M. Crowley et al[10]

This review article describes in depth about HME process and its operational requirements. Article mentions the following characteristics as the key aspects of HME process.

The feedstock must have good flow properties. When this prerequisite is not met, the feedstock tends to form a solid bridge at the throat of the hopper resulting in erratic flow. The friction on the inner surface of the barrel is the driving force of the material feed, whereas the friction at the surface of the screw restricts forward motion of the material. Thus, the bulk density and particle shape of the raw material impact the feeding efficiency. Inconsistent material feed may

result in a 'surge' phenomenon that will cause cyclic variation in product quality. Solidified polymer components can block the channel if melting is incomplete and result in a surge of material around the blockage. The efficiency of the melting process depends on the polymer properties and the extruder design. Polymers are subjected to a mechanical shear stress imposed by the rotating screw, and the thermal stress due to the relatively high processing temperature and pressure. Under these conditions, polymers may undergo chain scission, depolymerization or thermal degradation.

B. Mu, M.R. Thompson[12]

The mechanism of melt granulation inside twin screw extruder was studied in regards to nucleation and growth. The contributions of screw for mechanical mixing was studied. Two different PEG binders were used to probe the importance of viscosity and droplet size. It was found that binder viscosity was an important variable and the original size of the binder particles when added to the process as solid blended with lactose, was equally influential on the granule growth. The results in the work show that the mechanisms of hot melt granulation for high shear mixers can be equally applied to the extruder and fluidized bed.

- **High Shear Mixers for Hot Melt technique**

Nejat Rahmanian et al[36]

Granulation of calcium carbonate powder in a Cyclomix using aqueous polyethylene glycol as the binder was used to study the melt granulation in high shear granulator. An increase in the granulation time has a great effect on granules strength, till equilibrium is achieved. Increasing granulation time led to a more densified granule. Higher impeller speeds give rise to more consolidation and compact granules with ow porosity. As the binder viscosity is increased, the strength decreased and its distribution widens due to poor dispersion of binder in the powder bed. A higher binder viscosity produced strong inter-particle bridge, which gives rise to a low tendency for deformation and consolidation. No considerable effect on granule strength or PSD was observed by using different binder addition method, i.e. pouring at once and injecting.

Viviane Nart et al[37]

A modified-release (MR) tablet of the anti-anxiety drug pregabalin (PRE) was prepared by hot-melt coating PRE with glyceryl behenate (GB) as a release retardant and compressing to form a matrix with microcrystalline cellulose (MCC) as a hydrophilic diluent. GB was melted at 80 - 90°C in a vertical granulator (FM-VG-5P; Powrex, Osaka, Japan), PRE was added while shearing with impeller at 300 rpm and chopper at 2000 rpm, and then the melted mass was cooled down to 20°C and passed through no. 20#. The most-promising MR tablet batch was found to be stable for 6 months in an accelerated stability test and displayed pH-independent drug release that conformed to a first-order kinetic model. This study demonstrated potential use of GB for PRE containing MR formulations by hot melt granulation.

- **Fluidized Hot Melt Granulation**

Chirangano Mangwandi et al[38]

The overall aim of the work was to study he influence of process variables on the distribution of model drug during fluidization melt granulation. Granules were produced with lactose as diluent and PEG 1500 as meltable binder. Granulation time had a little impact on the granule homogeneity, but fluidization air velocity and temperature had a strong influence. The increase in fluidization air velocity results in breakage which lead in a more homogeneous product. Fluidization air temperature is thought to have influence on availability of binder for granulation process since, the viscosity of the binder droplets formed increases with increasing fluidized bed temperature. The strength of the nuclei formed is also a function of binder viscosity. It was concluded from the trials that a high level of homogeneity of the API in the granules could be achieved through FHMG.

Ivana Masic et al[22]

The article is aimed at studying the spray-on and *in situ* binder addition methods on characteristics of the granules obtained by FHMG. The observations suggest that regardless of the binder addition method, smaller binder particles/droplets size will result in quite narrow

particle size distribution. Also, both procedures showed good flow properties and similar trends in terms of granules size indicating that the controlling the particle/droplet size of binder can help in controlling the particle size of granules. It was observed that a higher binder content resulted in better granule flowability. The results suggested that melt granulation in fluidized bed could be a good alternative to conventional granulation technique.

G.M. Walker et al[39]

Co-melt granulation of lactose and PEG was investigated in a fluidized bed granulator. The effect of process parameters such as binder content and binder viscosity were correlated to granulation time and particle size distribution. The experimental data indicated that after initial nucleation, the granulation mechanism depends on binder content and binder viscosity. When the binder content is more than 18%, defluidization of the bed occurs. It was observed that after 10 min of granulation, only a slight increase in the granule size at PEG 10% was observed. It was also found that an increase in binder content narrows down the particle size distribution. The results suggested that increase in binder viscosity from 100-500mPa resulted in a significant decrease in granule growth rate.

R. Kraciuk, M.Sznitowska[40]

The objective of this study was to investigate the properties of granules and tablets with carbamazepine which were prepared employing FHMG technique. The FHMG process was carried out at 65°C. When the drug content was 30% (*w*/*w*), the yield of the process was satisfying (>95%) and flowability of the granules was better than placebo granules or drug-loaded granules prepared by wet granulation. Type of a filler had strong impact on physical properties of granules, and size distribution of the particles was the most homogenous when lactose or Di-Cafos were used. The FHMG technique enabled preparation of granules with better compressibility compared with the wet-granulated product or with non-granulated powders. In comparison to tablets prepared from the wet-granulated mass, employment of the FHMG method resulted in tablets with faster dissolution of carbamazepine (more than 80% of the drug released within 15 min). This was achieved with mannitol or lactose/MCC, as fillers.

Mašić I. et al[41]

The aim of this study was to investigate the influence of binder content, binder particle size, granulation time and inlet air flow rate on granule size and size distribution, granule shape and flowability, as well as on drug release rate. Hydrophilic (polyethylene glycol 2000) and hydrophobic meltable binder (glyceryl palmitostearate) were used for in situ fluidized hot melt granulation. Granule size was mainly influenced by binder particle size. Binder content was shown to be important for narrow size distribution and good flow properties. Granule shape was affected by interplay of binder content, binder particle size and granulation time. The results of the present study indicate that fluidized hot melt granulation is a promising powder agglomeration technique for spherical granules production.

Patent (Hot melt granulation technique):

EP 2 136 792 B1[42]

The present invention relates to a new method for making micropellets which comprise one or more binders and a pharmaceutically active ingredient. In particular, the invention has utility in increasing the solubility of poorly soluble pharmaceutically active ingredients. Melt palletization was used for the preparation of pellets comprising a pharmaceutically active ingredient wherein materials of low melting point (~40-100°C) are used as binders. The binders are typically either premixed with the powders and act as binders when heated above their melting point, or the binders are preheated, and sprayed whilst melted.

US 20140275242A1[43]

The present wok discloses a hot melt granulation formulation of poorly water-soluble active agent wherein the granule has an active ingredient and a wax dispersed therein, and the granules exhibits excellent friability when compressed to form a pharmaceutical composition.

US20090270448A1[44]

The present work discloses a pharmaceutical formulation of melt granule in the form of a solid dispersion of clopidogrel and PEG as carrier. The method of making melt granulate is that the carrier is mixed with the drug, and the mixture is heated to a temperature near to the melting point of the carrier thus forming a melt. The melt is cooled rapidly to provide congealed mass which s optionally milled to produce powder.

4.1 List of Material Used

Table 4.1 List of Materials used

Excipient	Property	Manufacture	Range (Handbook of Excipients)	IID (Maximum Potency as per May 2017)	
				Dose (Oral)	Dosage Form
Compritol 888ATO	Meltable Binder	Gattefosse, USA	>10%	142.5 mg	Tablet, ER
Hydrogenated Castor Oil	Meltable Binder	BASF, Germany	5-10%	187.5 mg	Tablet, SR
FlowLac 100	Diluent	Meggle, Germany	20-90%	708.9 mg	Tablet
Starch 1500	Diluent	Colorcon, USA,	5-75%	425.8 mg	Tablet
Avicel 102	Diluent	FMC, Ireland	20-90%	333.25 mg	Tablet, DR
PEG 6000	Pore Former	Clariant, India	10-15% (thermoplastic granulation)	86.4 mg	Tablet, ER
Magnesium Stearate	Lubricant	Covidien, USA	0.25-5%	53.8 mg	Tablet, DR

4.2 List of Equipment Used

Table 4.2 List of Equipments & Instruments used

Sr. No.	Equipment	Model No.	Make
1.	Electronic Weighing Balance	XP205MLT204	Mettler-Toledo Inc., Columbus, USA.
2.	Industrial Balance	M.T MonoBloc	Mettler-Toledo Inc., Columbus, USA.
3.	Turbula Blender	Turbula T2F	WAB (Willy A.Bachofen AG Maschinenfabrik), Mahopas, USA
4.	Fluidized Bed Drier	TG 200	Retsch, Hydrabad, India
5.	Tablet Compression Machine	Korsch XL	Silverwater, Australia
6.	Hardness tester	8M	Dr.Scleuniger Pharmatron, USA
7.	Ring Shear Tester	RST-XS	Dr. Dietmar Schulze, Wolfenbuttel, Germany
8.	Texture Analyzer	QTS25	Brookfield, USA
9.	Tap density Tester	TD 1025	Labindian, Mumbai, India
10.	Sieve Shaker	AS 200TAP	Retsch, Hydrabad, India
11.	Moisture Analyzer	HG 63 Halogen	Mettler-Toledo Inc., Columbus, USA.
12.	Fourier transform infrared Spectrophotometer (FTIR)	IRAffinity-1	Shimadzu, Japan
13.	USP Dissolution Apparatus - II	DS 8000	Labindia, Mumbai, India
14.	UV-Spectrophotometer	UV 1800	Shimadzu, Japan

Sr. No.	Equipment	Model No.	Make
15.	Stability Chamber	Newtronic stability Chambers	Newtronic Life Care equipment Pvt Ltd., Mumbai, India
16.	pH meter	PICO+	Labinidia, Mumbai, India
17.	Viscometer	DV2TLV	Brookfield, USA
18.	Co-mill	Quadro Co-mill	Quadro Engineering, Waterloo, Germany
19.	Flowdex	21-101-050	Hauson Research Corporation, USA
20.	Friability tester	Roche Friabilator	Labindia, Mumbai, India
21.	Vernier Digimatic Caliper	CD-6	Mitutoyo Corporation, Japan
22.	Differential Scanning Calorimetry	DSC-60	Shimadzu, Japan

4.3 Calibration Curves for Model Drug X

The aim of the work was to produce a modified release (MR) tablet. In a MR tablet, the complete release of the drug does not occur in gastric region. Thus, when gastric emptying occurs, the formulation faces a change in surrounding pH since the pH of the gastrointestinal tract is not uniform. Hence it is important to study the impact of different pH environments on dissolution profile of the drug from the formulation.

Therefore, calibration curves of Model Drug X in water, 0.1N HCl, 4.5 pH acetate buffer, 5.8 pH phosphate buffer and 6.8 pH phosphate buffer were prepared.

4.3.1 λ_{max} Determination

λ_{max} refers to the wavelength at which the molecule shows maximum absorbance. The Beer-Lamberts law works best when the absorbance is between 0.2-0.8. Hence, it is important to work with λ_{max} which gives the highest absorbance and thus avoids deviation from Beer-Lamberts law.

The λ_{max} determination was carried out as follows:

- A stock solution of 10 mg of Model Drug X in 100 ml of water (100 µg/ml) was prepared. 1 ml of stock solution was taken and the volume was made up to 10 ml to obtain the final solution (10 µg/ml).
- 10 µg/ml solution of Model Drug X in water was scanned over 400 - 200 nm using UV Spectrophotometer (UV 1800, Shimadzu; Japan) (**Fig. 4.1**)
- The wavelength at which maximum absorbance is obtained was selected as the detection wavelength (λ_{max}) for the Model Drug X. (**Table 4.3**)

Table 4.3 λ_{max} for Model Drug X

Wavelength (nm)	Absorbance
236.50	0.554

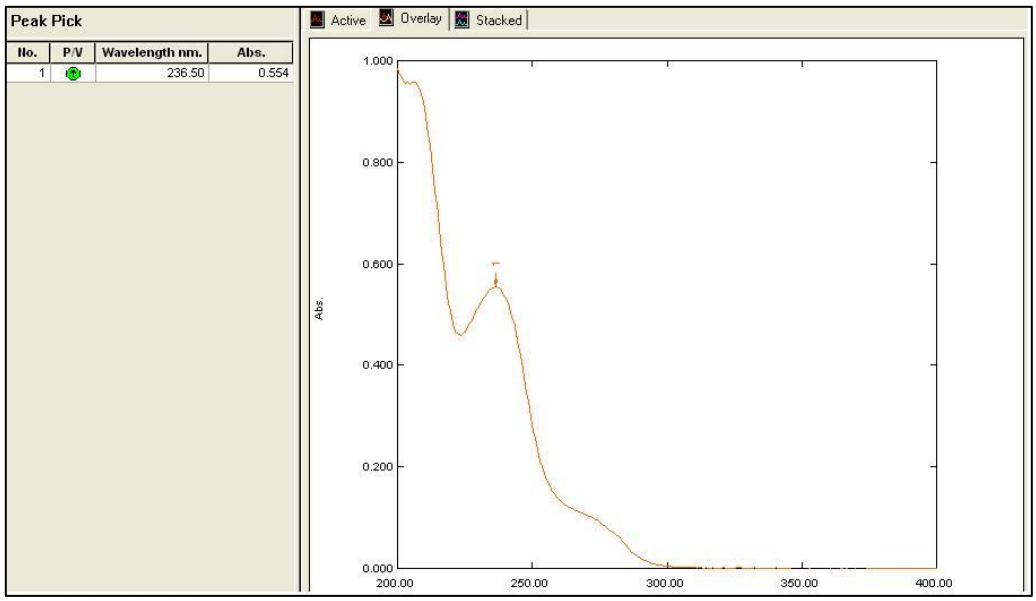


Fig. 4.1 UV Spectra of Model Drug X

Interpretation: The maximum absorbance was obtained at 237nm and thus it was selected as detection wavelength. Also, the λmax practically obtained matches the USP reference value for λmax (237nm) thus suggesting that the drug substance passes USP specifications.

4.3.2 Procedure for Calibration Curve Preparation

- 100 mg of model drug X was dissolved in 100 ml of 5.8 pH phosphate buffer (Stock Solution 1: 1000 µg/ml).
- 1 ml of stock solution 1 was diluted up to 100 ml (Stock solution 2: 10 µg/ml). This Stock solution 2 was used for further dilutions.
- 2, 4, 6, 8, 10ml of stock solution 2 were individually diluted to 10ml using 5.8 pH phosphate buffer (final solution).
- Same solutions (Stock 1, 2 and final solutions) were made using water, 0.1N HCl, 4.5 pH acetate, 6.8 pH phosphate buffer
- The absorbance of final solutions was taken using UV Spectrophotometer at 237 nm

4.3.3 Calibration Curve of Model Drug X in 5.8 pH phosphate buffer:

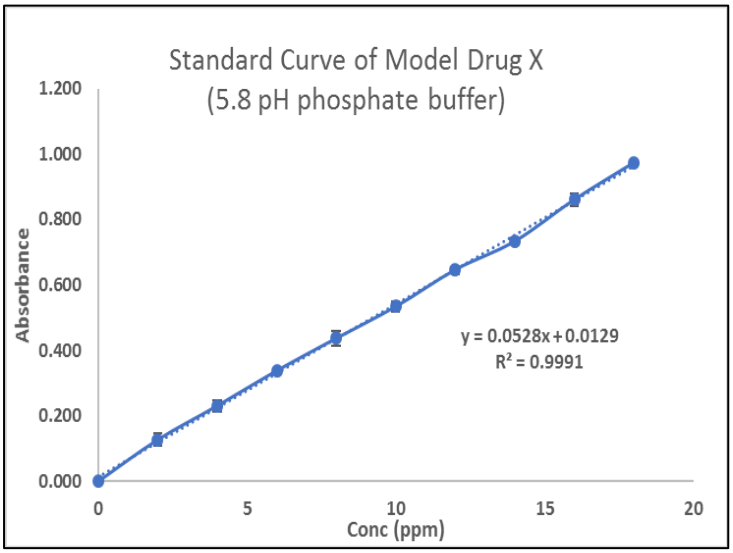


Fig.4.2 Calibration Curve in 5.8 pH phosphate buffer

Conc (ppm)	Mean Absorbance ± SD
0	0.000
2	0.127 ± 0.0203
4	0.231 ± 0.0168
6	0.338 ± 0.0031
8	0.437 ± 0.0271
10	0.534 ± 0.0144
12	0.646 ± 0.0121
14	0.733 ± 0.0104
16	0.861 ± 0.0200
18	0.973 ± 0.0026

Table 4.4 Absorbance in 5.8 pH phosphate buffer

Interpretation: The Standard Curve was found to be linear with a Correlation Co-efficient (R^2) of 0.9991 which shows good fit. The slope obtained from the equation is 0.0528.

4.3.4 Calibration Curve of Model Drug X in Water:

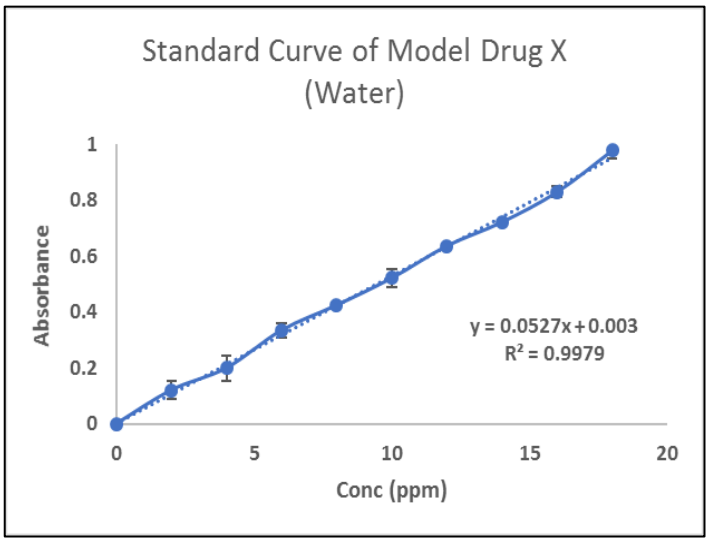


Fig.4.3 Calibration Curve in Water

Conc (ppm)	Mean Absorbance ± SD
0	0.000
2	0.144 ± 0.0314
4	0.247 ± 0.0451
6	0.359 ± 0.0240
8	0.424 ± 0.0060
10	0.556 ± 0.0335
12	0.634 ± 0.0031
14	0.725 ± 0.0023
16	0.853 ± 0.0199
18	0.963 ± 0.0277

Table 4.5 Absorbance in Water

Interpretation: The Standard Curve was found to be linear with a Correlation Co-efficient (R^2) of 0.9979 which shows good fit. The slope obtained from the equation is 0.0527.

4.3.5 Calibration Curve of Model Drug X in 0.1 N HCl:

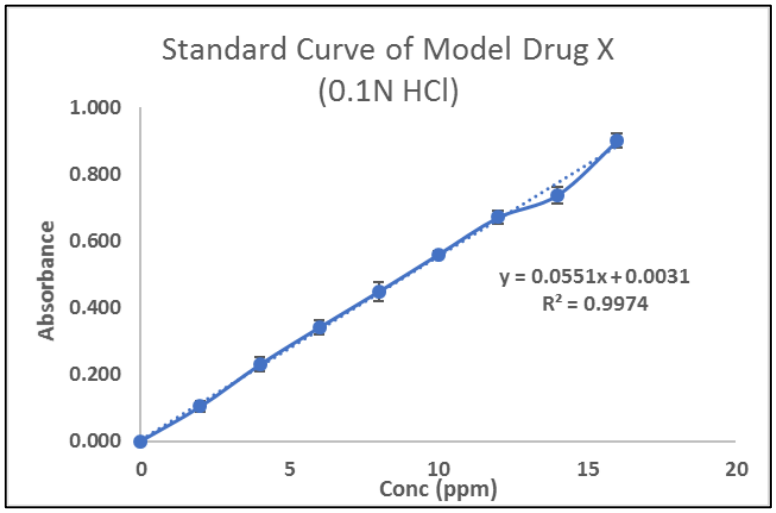


Fig.4.4 Calibration Curve in 0.1N HCl

Conc (ppm)	Mean Absorbance ± SD
0	0
2	0.104 ± 0.0148
4	0.229 ± 0.0221
6	0.341 ± 0.0205
8	0.449 ± 0.0280
10	0.560 ± 0.0095
12	0.671 ± 0.0200
14	0.738 ± 0.0252
16	0.900 ± 0.0200

Table 4.6 Absorbance in 0.1N HCl

Interpretation: The Standard Curve was found to be linear with a Correlation Co-efficient (R^2) of 0.9974 which shows good fit. The slope obtained from the equation is 0.0551.

4.3.6 Calibration Curve of Model Drug X in 6.8 pH phosphate buffer:

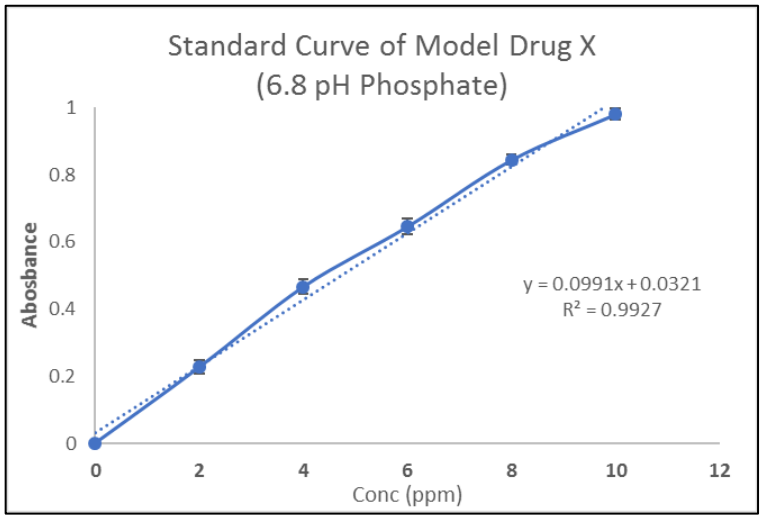


Fig.4.5 Calibration Curve in 6.8 pH phosphate buffer

Conc (ppm)	Mean Absorbance ± SD
0	0
2	0.227 ± 0.0209
4	0.467 ± 0.0209
6	0.646± 0.0245
8	0.845 ± 0.0153
10	0.981 ± 0.0172

Table 4.7 Absorbance in 6.8 pH phosphate buffer

Interpretation: The Standard Curve was found to be linear with a Correlation Co-efficient (R^2) of 0.9927 which shows good fit. The slope obtained from the equation is 0.0991.

4.4 Analysis of Reference Product

To successfully develop and manufacture a generic product, it is important that the product under development is pharmaceutically equivalent to a reference product which is already in market[45]. The aim this project was to produce a product using FHMG and determine whether FHMG can be used as an alternative to currently available techniques. Thus, it is important to match the dissolution profile of the Drug X to a currently available marketed product to show pharmaceutical equivalence. The details of the reference product are mentioned in **Table 4.8**

Table 4.8 Reference Product Details

Active Ingredient	Model Drug X
Strength	60 mg

Drug Release Profile of Reference Product

Since the reference product is also a MR tablet, it is important to perform the multimedia study so as to understand the effect of different pH environments in the drug release profile. The dissolution study parameters for Reference product are mentioned in **Table 4.9**. The drug release profile obtained is shown in **Fig. 4.6**

Table 4.9 Dissolution study parameters for Reference product

Dissolution Apparatus	USP Type II (Paddle)
Dissolution Media	Water, 0.1N HCl, 4.5 pH acetate buffer, 5.8 pH phosphate buffer, 6.8 pH phosphate buffer
Media Volume	900 ml
Media Temperature	37.0 ± 0.5°C
Paddle rotation speed	100 rpm
Sample Volume	10 ml
Sample Time points	0.5, 1, 2, 3, 4, 5 hours
Recovery	@150 rpm for 1 hour

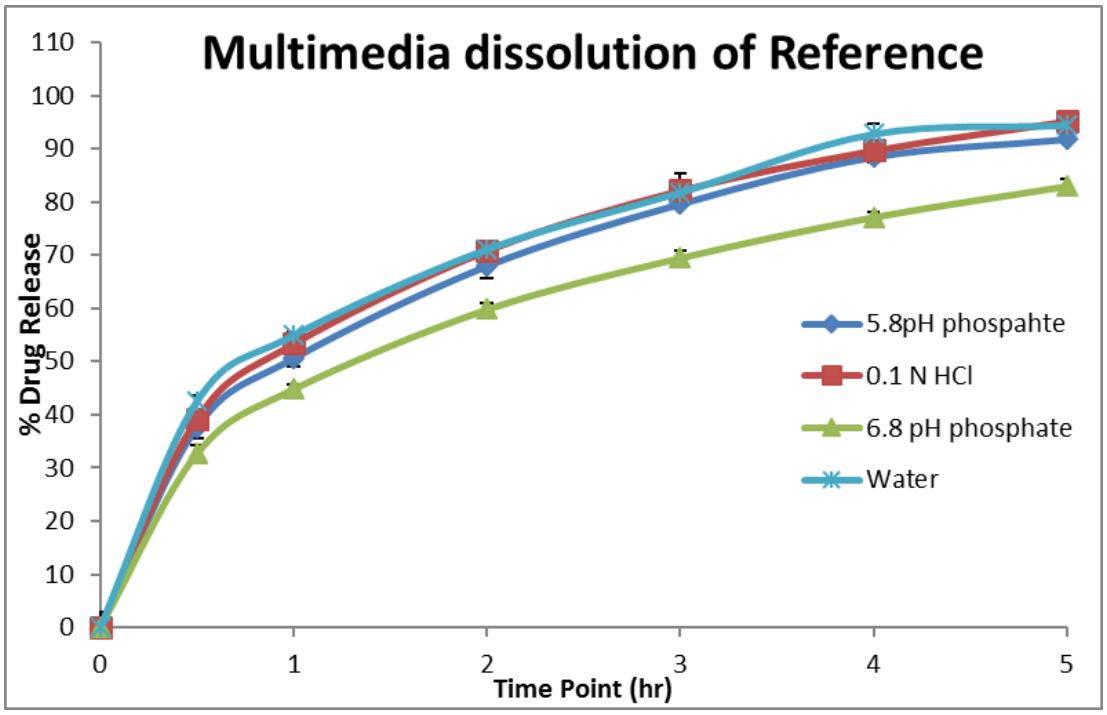


Fig.4.6 Multimedia Drug Release Profile of Reference Product

Discussion: From the multimedia study of the reference product (**Fig. 4.6**), it was observed that the Model Drug X has a pH-independent release profile.

Thus, 5.8 pH phosphate buffer was chosen as the dissolution media for the preliminary trial and during formulation development studies since the OGD media for Model Drug X is 5.8 pH phosphate buffer.

The multimedia study was carried out only for the optimized batch.

4.5 QbD Approach for Formulation Development[31]

QbD is based on inculcating quality into the product from the beginning than testing it in the product. To inculcate quality into a product, it is important to have a knowledge the requirements for the product design and performance in the early designing phase. These product requirements can be found in a Quality Target Product Profile (QTPP). In addition to defining the requirements to design the product, the QTPP help in identifying the critical quality attributes (CQAs) such as potency, uniformity in dosage form, purity, drug release, etc.

4.5.1 Quality target product profile (QTPP)

The QTPP for a product is determined from the desired performance of a new product.

Table 4.10 shows the QTPP for the development of MR tablets.

Table 4.10 QTPP for MR tablets

Quality Attributes of the Drug Product		Target (QTPP)	Is this a CQA ?	Justification
Dosage Form		Tablet	**No**	For patient acceptance and compliance**.**
Dosage Design		Modified Release Tablet	**No**	For better patient compliance and improved therapeutic effect
Route of Administration		Oral	**No**	For patient acceptance and compliance
Dosage Strength		60mg	**No**	For therapeutic effect
Physical Attributes	Appearance	Color and Shape acceptable to patient. No visual defects observed.	**No**	Appearance is not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.

Quality Attributes of the Drug Product		Target (QTPP)	Is this a CQA ?	Justification
Physical Attributes	Odor	No unpleasant odor	**No**	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability and lead to complaints. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Acceptable to patient and easy to swallow	**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 reference product.
	Friability	NMT 1.0%w/w	**No**	A target of NMT 1.0% mean weight loss is set according to the compendia requirement and to minimize damage to final product during packing or transport.
	Hardness	Similar to reference product	**No**	Hardness is not directly linked to safety and efficacy, but may have impact on friability and dissolution of tablets.
Assay		100.0% of label claim	**Yes**	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Uniformity of Dosage Unit		Conforms to USP <905> Uniformity of Dosage Units	**Yes**	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.

Quality Attributes of the Drug Product	Target (QTPP)	Is this a CQA ?	Justification
Dissolution (Drug release)		**Yes**	*In vitro* drug dissolution is indicative of *In vivo* performance. Failure to meet the dissolution specifications can impact bioavailability. Both formulation and process variables could affect the dissolution. This CQA will be investigated during formulation and process development.

4.5.2 Initial Risk Assessment[33]

A systematic risk assessment was performed on the basis of literature to identify and rank parameters which may have a potential to have an impact on product quality. The relative risk of these CMAs and CPP was ranked as high, medium, or low. Those attributes that are ranked high have great impact on the product CQAs and thus need further investigation, whereas those attributes that had low impact on the product CQAs need no further investigation. **Table 4.11** summarizes the relative risk ranking system.

Table 4.11 Overview of relative risk ranking system

Risk	Acceptability	Action to be taken
Low	Broadly acceptable risk	No further investigation is needed
Medium	Risk is accepted	Further investigation may be needed in order to reduce the risk
High	Risk is unacceptable	Further investigation is needed to reduce the risk

4.5.2.1 Initial Risk Assessment of Drug substance attributes

The selection of appropriate salt, solid state form (amorphous, polymorph), particle size and flow properties of API will impact CQAs such as solubility, dissolution rate, chemical and physical stability as well as manufacturability. Thus, it is important to study these attributes to produce a product with desired safety and efficacy. **Table 4.12** shows the risk assessment for the Drug substance attributes on the product CQAs and **Table 4.13** gives the justification for the same.

Table 4.12 Initial Risk Assessment of Model Drug X

Drug Substance Attributes	Drug Product CQAs		
	Assay	Uniformity of Dosage Unit	Dissolution
Solid State Form	Low	Low	Medium
Particle Size Distribution	Medium	Medium	Medium
Flow Properties	Low	Low	Low
Hygroscopicity	Low	Low	Low
Moisture Content	Low	Low	Low

Table 4.13 Justification for risk assessment of the drug substance attributes

Drug Substance Attributes	Drug products CQAs	Risk	Justification
Solid state Form	Assay	Low	Solid state of drug substance does not affect tablet assay. Hence, risk is rated low
	Uniformity of Dosage Unit	Low	Since the development of the tablet is done by granulation process, solid state of the drug does not have an impact on the uniformity of the dosage unit. Therefore, the risk is low.

	Dissolution	Medium	There are no polymorphs reported for API in Literature (API-DMF). But amorphous and crystalline forms of the drug are available which have different solubility. This can impact the dissolution profile. However, the DMF holder consistently provides crystalline form of specified PSD. Retention of this form in drug product has to be studied during development
PSD (Particle Size Distribution)	Assay	Medium	PSD may adversely impact the blend flowability which may cause inconsistency in assay and uniformity of the dosage unit. However, the development of the tablet is done by melt granulation process in which inconsistency of assay and uniformity of dosage unit is unlikely. Based on the further studies the risk will be revisited.
	Uniformity of Dosage Unit	Medium	
	Dissolution	Medium	Since the drug belongs to BCS class I, a minor change in the PSD of the drug will not affect the dissolution. However, a major difference between batches with to PSD may have an impact on the dissolution. Thus, the risk is rated medium.

Flow Properties	Assay	Low	API flow properties may impact the blend flow which may cause inconsistency in assay and uniformity of dosage unit. However, here melt granulation process was adopted in which inconsistency of assay and uniformity of dosage unit is unlikely. So, the risk is rated as low.
	Uniformity of Dosage Unit	Low	
	Dissolution	Low	API flow does not have any impact directly or indirectly on the dissolution profile of the drug product. So, the risk is rated low.
Hygroscopicity	Assay	Low	API is non-hygroscopic in nature. So, the risk is low.
	Uniformity of Dosage Unit	Low	
	Dissolution	Low	
Moisture Content	Assay	Low	Moisture is controlled in the drug substance specification (NMT 0.5%). Thus, it is unlikely to impact assay, uniformity of dosage unit and dissolution. Therefore, the risk is low.
	Uniformity of Dosage Unit	Low	
	Dissolution	Low	

4.5.2.2 Initial Risk Assessment of CMA

A systematic risk assessment was performed on the basis of literature [38,46,47,48] to identify and rank parameters which may have a potential to have an impact on product quality. Understanding of the material attribute used to formulate a dosage form is critical to product performance. A clear justification of why the particular types, grades, and amounts of excipient is selected for formulation development is important. The knowledge of which material attributes contributes most to product performance may help in development of product in a more systematic way with reduced number of trials. **Table 4.14** shows the risk assessment for the critical material attributes on the product CQAs and **Table 4.15** gives the justification for the same.

Table 4.14 Initial Risk Assessment of Formulation Variables

Formulation Variables	Drug Product CQAs		
	Assay	Uniformity of Dosage Unit	Dissolution
API particle size distribution	Medium	Medium	Medium
Filler	Low	Low	High
Hydrophobic Binder	Low	Medium	High
Pore Former	Low	Low	High
Lubricant	Low	Low	Low

Table 4.15 Justification for the initial risk assessment of the formulation variables

Formulation Variables	Drug Product CQAs	Risk	Justification
API PSD	Assay	Medium	

Formulation Variables	Drug Product CQAs	Risk	Justification
	Uniformity of Dosage Unit	Medium	PSD may adversely impact the blend flowability which may cause inconsistency in assay and uniformity of the dosage unit. However, the development of the tablet is done by melt granulation process in which inconsistency of assay and uniformity of dosage unit is unlikely. Based on the further studies, the risk will be revisited.
	Dissolution	Medium	Since the drug belongs to BSC class I, a minor change in the PSD of the drug will not affect the dissolution. However, a major difference between batches with to PSD may have an impact on the dissolution. Thus, the risk is rated medium.
Filler	Assay	Low	Filler in granulation process is known to result uniform distribution of drug substance and excipients. Thus, it is unlikely to affect assay and uniformity of dosage unit of drug product. Hence, the risk is rated as low.
	Uniformity of Dosage Unit	Low	
	Dissolution	High	Filler's hydrophilic or hydrophobic nature may impact granule properties, which could have impact on drug release properties from the drug product. Hence, the risk is rated as high.
Hydrophobic Binder	Assay	Low	Concentration of hydrophobic binder affects particle size distribution of granules which is unlikely to affect the assay of drug product. Hence, the risk is low.

Formulation Variables	Drug Product CQAs	Risk	Justification
	Uniformity of Dosage Unit	Medium	Concentration of hydrophobic binder affects particle size distribution of granules which is likely to affect the uniformity of drug product. Hence, the risk is medium.
	Dissolution	High	Hydrophobic Binder concentration may impact granule properties and tablet disintegration, which have an impact on drug release properties from the drug product. Hence, the risk is rated as high.
Pore Former	Assay	Low	Concentration of pore former affects particle size distribution of granules which is unlikely to affect the assay and uniformity of dosage unit of drug product. Hence, the risk is low.
	Uniformity of Dosage Unit	Low	
	Dissolution	High	Pore former is responsible for the channel formation in the matrix, which in turn has impact on drug release from the drug product. Hence, the risk is rated as high.
Magnesium Stearate	Assay	Low	Magnesium stearate is used as lubricant in low content (0.5%). At this level, it is unlikely to impact to impact assay, uniformity of dosage unit and dissolution. The risk is low.
	Uniformity of Dosage Unit	Low	
	Dissolution	Low	

4.5.2.3 Initial Risk Assessment of CPA

A systematic risk assessment was performed on the basis of literature to identify and rank parameters which may have a potential to have an impact on product quality.[47,48,49,50] The Risk assessment of the process variables is most to understand which variable has the most impact on the CQAs of the product. This helps in minimizing the trials needed for the formulation of the product and accurately screens out the variables which need the maximum attention while optimization of the product. **Table 4.16** shows the risk assessment for the process variable on the product CQAs and **Table 4.17** gives the justification for the same.

Table 4.16 Initial Risk Assessment of Process Variables

Process Variables	Drug Product CQAs		
	Assay	Uniformity of Dosage Unit	Dissolution
Sifting	Low	Low	Low
Granulation: Time	Low	Low	High
Granulation: Fluidization Air Temperature	Low	Low	High
Granulation: Fluidization Air Velocity	Medium	Medium	Low
Milling	Low	Low	Medium
Blending & Lubrication	Low	Low	Low
Compression	Medium	Medium	High

Table 4.17 Justification for the Initial Risk Assessment of the Process Variables

Process Variables	Drug Product CQA's	Risk	Justification
Sifting	Assay	Low	API and excipients easily pass through 40# sieve. However, appropriate covering of gasket

Process Variables	Drug Product CQA's	Risk	Justification
	Uniformity of Dosage Unit	Low	and sieves controls the loss due to dusting. Thus, the impact on the CQAs of this process variable is unlikely.
	Dissolution	Low	
Granulation: Time	Assay	Low	In granulation process, inconsistency in assay and CU is unlikely due to binding of API with excipients. Hence risk is rated low.
	Uniformity of Dosage Unit	Low	
	Dissolution	High	Granulation time directly impacts the interaction time between meltable binder and API; thus affecting the coating of the binder on the API particles which in turn has an effect on the dissolution profile. Thus, the risk is rated high.
Granulation: Fluidization Air Temperature	Assay	Low	API is stable with heat and unlikely to have impact on all these CQAs.
	Uniformity of Dosage Unit	Low	
	Dissolution	High	Since the granulation temperature directly impacts the melting of the binder, it affects the coating of the binder on the API particles and thus has an effect on the dissolution profile. Thus, the risk is rated high.
Granulation: Fluidization Air Velocity	Assay	Medium	At high air flow, assay of the product may reduce due to drug loss. Thus, the risk has to be revisited and is rated medium
	Uniformity of Dosage Unit	Medium	A higher air velocity can cause excessive particle attrition and can damage binder coat on the API. Hence, the risk is medium.

Process Variables	Drug Product CQA's	Risk	Justification
	Dissolution	Low	Fluidization air velocity is not likely to impact the dissolution of the product since the final PSD is governed by milling process.
Milling	Assay	Low	The milling step controls the final granule size distribution. Uniform distribution of granules may not affect granules flow-property during compression process. Hence, the inconsistency in CU and Assay is unlikely.
	Uniformity of Dosage Unit	Low	
	Dissolution	Medium	PSD of the granules present in the end formulation determine the surface area for drug release. Milling has an impact on this PSD. But in a matrix tablet, PSD of the granules do not have a major impact the release profile. Thus, this risk has to be revisited.
Lubrication	Assay	Low	Lubrication is mixing step for lubricant with blend before compression. Lubrication time and blender speed is unlikely to impact these drug product CQAs. Hence, the risk is low.
	Uniformity of Dosage Unit	Low	
	Dissolution	Low	Magnesium stearate is used as lubricant in low content (0.5%) and for a standard time (3min). At this level and for this time, it is unlikely to impact to impact dissolution. The risk is low.
Compression	Assay	Medium	A faster than optimal press or suboptimal speed could likely result in die filling and weight variability which may impact tablet assay and CU. Hence, the risk is rated as medium.
	Uniformity of Dosage Unit	Medium	

Process Variables	Drug Product CQA's	Risk	Justification
	Dissolution	High	Hardness of tablets can impact on drug release from drug product. Hence, the risk is rated as high.

4.6 Preformulation Study

Preformulation study is the first step in the systematic development of the final dosage form. It involves investigation of physical and chemical characteristics of drug substance alone and when combined with excipients.

4.6.1 Evaluation of Physiochemical Characteristics of drug

Physical and chemical evaluation of drug is important for stable, efficacious and safe formulation development. **Table 4.18** show the physiochemical characteristics of drug.

Table 4.18 Model Drug Characterization

Test		Observations	USP specification
Description		White, odorless, crystalline powder	White, odorless, crystalline powder or small crystals
Melting Points		Melts at 212°C - 213°C	Melts at about 210°C
Assay		99.6%	98.5 – 101.5%
Residue on Ignition		0.02%	NMT 0.10%
Heavy Metal		Less than 20 ppm	NMT 20 ppm
Loss on Drying		0.18%	NMT 0.50%
Residual Solvents (RS)	Class 2 RS:		
	1. Toluene	302 ppm	NMT 750 ppm
	2. Methanol	284 ppm	NMT 500 ppm
	Class 3 (RS):		
	1. Isopropyl Alcohol	2 ppm	NMT 1000 ppm
	2. Ethyl Acetate	1 ppm	NMT 500 ppm
Total Impurities		0.02%	NMT 0.50%
Particle Size Distribution	D10	5µ	-
	D50	26.11µ	
	D90	87.69µ	

4.6.2 FTIR Spectra of Model Drug X

Every molecule consists of various chemical groups which vibrate and produce signals when exposed to infrared rays. These signals are used to test the purity and for the identification of chemicals.

FTIR spectra of Model Drug X in KBr pellets at optimum scanning speed between 4000-400 cm-1 was carried out using FTIR (IRAffinity-1, Shimadzu, Japan). The observed peaks were compared with standard. **Fig. 4.7** shows the FTIR spectra of the Model Drug X which characteristics peaks. **Table 4.19** shows the comparison of practically obtained and theoretical FTIR frequencies.

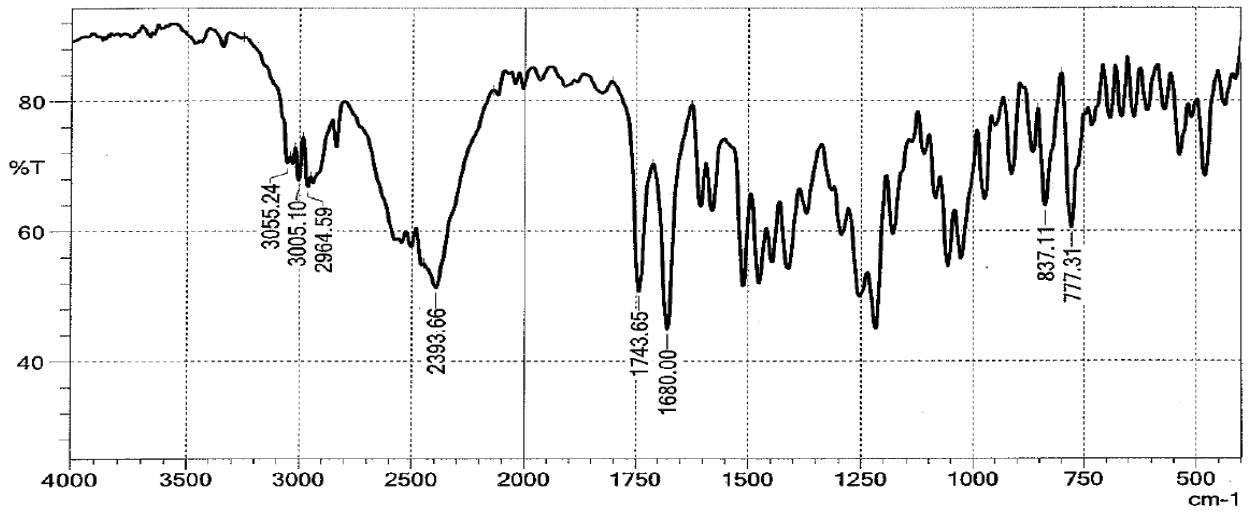


Fig.4.7 FTIR Spectra of Model Drug X

Table 4.19 FTIR frequency of Model Drug X

Functional Group	Obtained Value (cm^{-1})	Theoretical Range (cm^{-1})
Ester C=O	1743.65	1735 - 1750
Amide C=O	1680.00	1690 – 1630
Aromatic Ring	837.11	850-750

Interpretation: From the FTIR spectra and frequency table, we can conclude that the obtained peaks of the critical functional groups of the Model Drug X are within the theoretical range. This also suggests that the drug is pure.

4.6.3 DSC graph of Model Drug X

DSC is a technique used to study the chemical changes in a substance when they are heated. These changes are important to understand the behavior of a substance when they are exposed to increased temperature. As the temperature is increased the sample eventually reaches its melting point and eventually may decompose. Since the FHMG process involves temperature application, it is important to study the behavior of the API when it is exposed to temperatures equal to and above the melting point. The DSC curve for Model Drug X is shown in **Fig. 4.8**

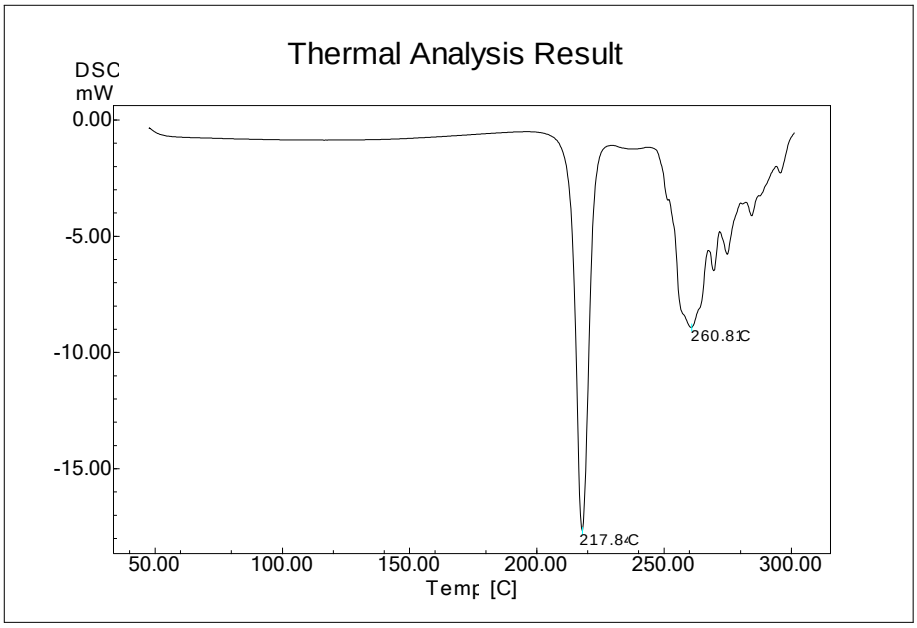


Fig.4.8 DSC curve for Model Drug X

Interpretation: A primary endotherm corresponding to melting point was observed at 217°C. This matches to the theoretical melting point of the drug which is 212 – 217°C. This suggests the purity of the drug.

The DSC curve shows decomposition which is apparent from 240°C. This indicates that the processing temperature during granulation should be below 240°C. A temperature higher than this will leading to decomposition of the drug.

4.6.5 Drug Excipient Compatibility

Drug Excipient Compatibility study was carried out on all the initially chosen excipients for the formulation development. This study is carried out to understand if there is any unwanted interaction between the selected ingredients with respect to different temperature and relative humidity conditions. Any significant change in the physical appearance (discoloration, agglomeration, etc) or chemical change (FTIR, DSC, etc) is not acceptable. The IR spectra of pure drug and physical mixture of drug and excipients was obtained by the KBr mixture pellet technique.

Following is the protocol for Drug Excipient compatibility study-

1. **Packaging Details**

   Samples with API and excipients will be packed in glass vial in open and closed conditions.

   Closed Condition: - Clear Glass vial closed with Teflon stopper and sealed with aluminum cap. The bottles should be in the upright position in the stability chambers.

   Open Condition: **-** Clear Glass vial without Teflon stopper and aluminum cap covered by perforated Para film.

2. **Sampling Plan**

   Sampling plan will include:

   Excipients alone,

   API alone,

   Excipients and API Binary Mixture.

3. **Sample preparation**

- Excipient and API alone are to be filled in glass vials directly.
- Excipient and API in ratio are to be sifted using ASTM #30 & 60# sieve, mixed and filled in the glass vials.

4. Plan for stability charging

The compatibility studies were performed as per ICH guideline. The samples were kept at two conditions namely, 25°C / 60% RH for 2 weeks and 40°C / 75% RH for 4 weeks. Both open and closed samples were placed at both conditions. **Table 4.20** shows the details of samples and samples placed at different conditions.

Table 4.20 Drug Excipient Compatibility Sample and Conditions

Sample details	Condition	No. of Samples per Condition	Initial	2 W		4 W		No of vials
				Open*	Close#	open	close	
API alone	25°C/60%RH	1	√	√	√	-	-	3
Excipients alone	25°C/60%RH	7	√	√	√	-	-	21
Binary mixture (1:0.5)	25°C/60%RH	7	√	√	√	-	-	21
API alone	40°C/75%RH	1	-	√	√	-	-	2
Excipients alone	40°C/75%RH	7	-	-	-	√	√	14
Binary mixture (1:0.5)	40°C/75%RH	7	-	-	-	√	√	14
Total number of samples		**30**						**75**

* '√' : Sample kept at that condition

'-' : No sample at that condition

5. Test

- Visual appearance and impurities at each time point is determined. Samples to be pulled at the time points from each storage conditions should be taken for testing.
- Initially analysis would be carried out for Open samples and the closed samples were analyzed further by FTIR.

Result

The visual evaluation of the samples showed no change in the physical properties. That is, there were no color change or agglomerations found in the sample. The samples were free flowing powders. Thus, the samples were further evaluated by FTIR.

FTIR spectra of Model Drug X in KBr pellets at optimum scanning speed between 4000-400 cm-1 was carried out using FTIR (IRAffinity-1, Shimadzu, Japan). The observed peaks were compared with standard. The **Table 4.21** shows the comparison of characteristic peaks that obtained practically and that reported in the literature.

Table 4.21 Result for Drug Excipient Compatibility Study

Characteristic IR peaks of Drug X and Drug X – Excipient (cm $^{-1}$)								
Pure Drug X (Theoretical Range)	Drug X (Obtained)	Drug + Compritol	Drug + HCO	Drug + MCC	Drug + Starch 1500	Drug + Lactose Monohydrate	Drug + PEG 6000	Drug + MgS
1735 - 1750 (ester C=O)	1743.65	1743.65	1743.65	1743.65	1743.65	1743.65	1743.65	1743.65
1690 –1630 (amide C=O)	1680.00	16800.00	1680.00	1680.00	1680.00	16800.00	1680.00	1681.93
850-750 (aromatic ring)	837.11	839.03	839.03	839.03	839.03	837.11	839.03	839.03

Conclusion from drug excipient compatibility studies:

All the selected excipients were found to compatible with the drug since no change in the physical appearance and no interaction of peaks in the FTIR spectra was observed.

4.7 Formulation Development

4.7.1 Preliminary Trials for Formulation Variable

Based on the initial risk assessment it can be concluded that Binder, Pore Former and Filler are the formulation variables that have a potential high impact on the CQAs. Thus, a one factor at a time (OFAT) approach was used to optimize these variables.

4.7.1.1 Binder Screening Trials

Table 4.22 Feasibility Trial Batch Formula

Sr. No	Ingredient	Quantity (%w/w)	Quantity (mg)		Role
			Trial 1	Trial 2	
1	Model Drug X	30	60	60	Active Ingredient
2	Hydrogenated castor oil	15	30	-	Hydrophobic Binder
	Compritol 888 ATO	15	-	30	
3	Lactose Monohydrate	54.5	109	109	Filler
5	Magnesium Stearate	0.5	1	1	Lubricant
Total Tablet Weight		100%	200 mg		

Procedure:

1. All ingredients (except Magnesium Stearate) mentioned in **Table 4.22** were weighed accurately and Sifted through 30#.
2. Weighed ingredients were transferred in a FBD bowl.
3. Dry mixing of the blend was done in FBD at minimum fluidization (10 CFM) for 30 sec.
4. After 30 secs, the temperature of FBD was increased to 10°C above the melting point of meltable binder (maintaining the fluidization at minimum value).
5. After the completion of granulation, the temperature of FBD was reduced to get the product to room temperature with maximum fluidization (fluidization at 40-50 CFM).

6. The material was removed from FBD and granules were sifted through 20#.
7. The 20# retained granules were co-milled and mixed with the remaining blend.
8. The blend was lubricated with 0.5% Magnesium Stearate (40# passed) and compression was carried out on Korsch XL.

Results:

1. **Melt Viscosity of the meltable binders:**

   Melt viscosity is the viscosity of the binder at melting point. So, to find out the melt viscosity, the meltable binder was first melted on a hot plate till it melts. When the melting point is achieved, the viscosity of the molten binder was measured using a Brookfield viscometer.

   Melt Viscosity of Compritol 888 ATO was found to be 8 - 10cps and that of HCO was 12-13cps.

2. **Particle Size Distribution:**

   Fig. 4.9 (a) & 4.10 (a) show the granules appearance for the trials with different binders. Trial 1 with HCO as binder shows higher number of granules as compared to Trial 2. Particle size distribution analysis before co-milling step (granules obtained after granulation) was carried using Retsch Sieve Shaker. The analysis was done for 5 min using 100 gm of granule blend. **Fig. 4.9 (b) & 4.10 (b)** show the graph for the particle size distribution for granules with HCO and Compritol respectively.

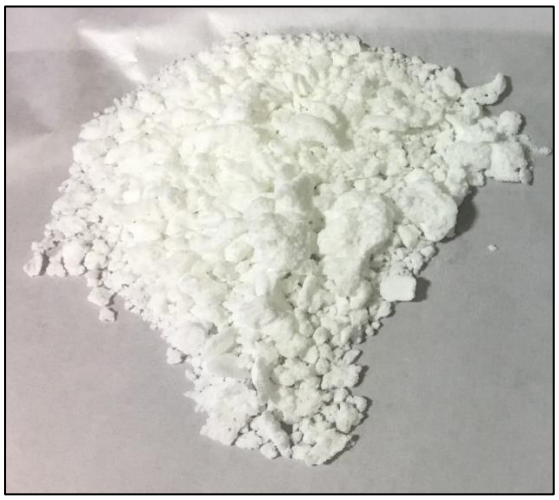


Fig.4.9 (a) Granule Appearance for Trial 1

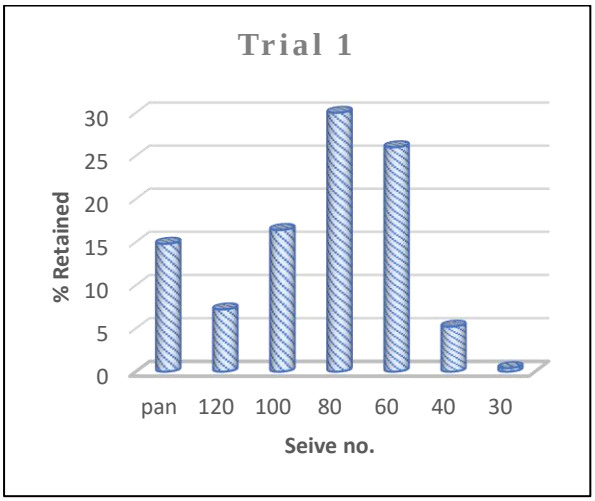


Fig.4.9 (b) PSD for Trial 1 with HCO as binder

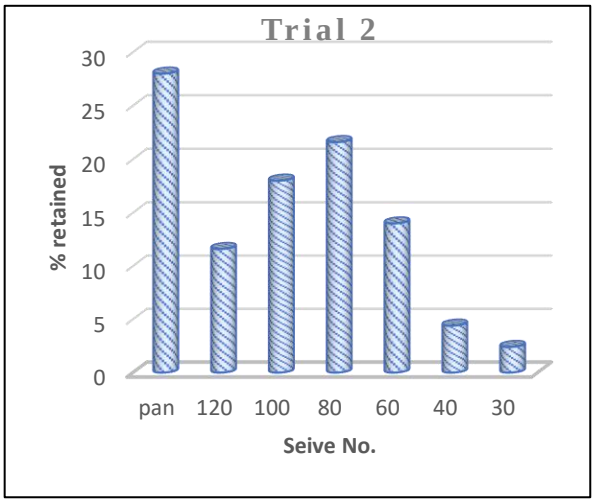


Fig.4.10 (a) Granule Appearance for Trial 2 **Fig.4.10 (b) PSD for Trial 2 with Compritol as binder**

Discussion: The Trial 1 (with HCO as binder) had lesser % of fines as compared to Trial 2 (with Compritol as binder). This may be attributed to the melt viscosity of the binder, since it defines the binding capacity of the binder. Lesser melt viscosity of Compritol 888 ATO can be attributed to the higher ratio of the fines produced after granulation.

3. **Flow Properties:**

Flow properties of the powders were tested using Tap density tester (TD 1025) by Labindia. The USP method I - graduated cylinder was followed i.e. 500 taps and 750 taps with 50 gm of granule blend. **Table 4.23** compares the flow properties obtained from the trials with the two different binders

Table 4.23 Flow Properties for Trials with different binders

Parameter	Trial 1 (with HCO as Binder)	Trial 2 (with Compritol as Binder)
Bulk Density	0.51	0.51
Tapped Density	0.60	0.63
Compressibility Index	15.5	20.00
Hausner's Ratio	1.18	1.25
Inference	**Fair to Good Flow**	**Fair Flow**

4. Assay in different size fraction:

It is important to study the distribution of the drug in the different granules size as it affect the uniformity of the dosage for and also gives an idea whether or not the mixing of the powder is occurring efficiently. **Table 4.24** shows the assay for the different size fractions obtained from sieving the granulated blend through different mesh sizes.

Table 4.24 Assay in different granule size fraction

Assay % (±SD)	Particle Size Fraction	Assay % (±SD)
100.7 ±0.9	0-250µm	101.6 ±0.5
99.8 ±0.6	250-600µm	99.4 ±0.7
97.9 ±0.4	>600µm	99.1 ±0.6

Discussion: All the size fractions in the both in the binder showed a comparable assay. This suggests a uniform mixing/distribution of drug in different size fractions of the granulated blend.

5. Determination of Compressibility:

Table 4.25 Desired Tablet Parameters

Weight	200 mg ± 5%
Thickness	4.27 mm ± 5%
Diameter	7.9 mm

Table 4.26 Compression Parameters for MR tablet of Drug X

Machine	Korsch XL
Cam Track	4 – 10 mm
Tooling	B, round, standard concave punches
Die Diameter	7.9 mm
Turret Speed	20 rpm

- The compression was carried out as per the parameters mentions in **Table 4.26.**

- The weigh was first optimized to 200 mg (**Table 4.25**) and then study was further continued to find out the maximum hardness that could be achieved by the two trial batches.
- 10 tablets were randomly selected from the two batches and a weight variation test was carried out. The results are shown in **Table 4.27.**

Table 4.27 Weight Variation test for batches with different binder

Parameter	Trial 1 (HCO as binder)	Trial 2 (Compritol as binder)
Average Weight	200.02 mg	200.11 mg
SD	1.46 mg	0.90 mg
RSD	0.73%	0.45%
Min	198.0 mg	198.9 mg
Max	203.2 mg	201.8 mg

- Maximum hardness that could be achieve with Compritol 888 ATO (Trial 2) was 4.0 - 4.5Kp while that with HCO (Trial 1) was 7.0 - 7.5Kp

6. Dissolution Profile:

The dissolution study was performed as mention in δ4.4. The results of the same are shown in **Table 4.28**

Table 4.28 Dissolution Profile for Trials with different Binders

Batch#	Trial 1		Trial 2	
Time points (hr)	**% Drug Release**	**%RSD**	**% Drug Release**	**%RSD**
0.5	30.1	0.6	31.7	1.9
1	34.5	2.3	35.2	1.2
2	41.1	1.8	40.6	1.4
3	49.6	2.4	49.2	0.2
4	56.3	2.1	57.8	0.5
5	62.3	0.7	64.5	0.1

Discussion: The release profile for both the binders showed no major difference with respect to the % drug released at various time point (**Table. 4.28**). Thus, suggesting a comparable and equal release controlling capacity of the two binders.

Also, an important observation here was that even after 5hrs, only about 65% of the drug is released.

Conclusion from preliminary batch trials for meltable binder selection:

Both binders showed the similar release controlling properties and near to 100% assay in the different size fractions of the granulated blend. The weight variation test shows that there was uniformity of dosage unit for both the batches.

But Trial Batch 1 (with HCO as binder) showed better compressibility, better flow properties and better particle size distribution as compared to Trial Batch 2 (with Compritol as binder).

Hence, HCO was chosen as the final binder and the further batches were conducted with the same. The amount of HCO would be reduced to 28mg in further trials so as to combat the issues of incomplete release from the formulation.

Also, dissolution study suggests a need for addition of a pore forming agent which would help in increasing the drug from the hydrophobic matrix. A Trial was planned with Polyethylene 6000 to study the effect of a pore former.

4.7.1.2 Effect of Pore Former

An important observation from the dissolution study was that even after 5hrs, only about 65% of the drug is released. This suggests a need for addition of a pore forming agent which would help in increasing the drug from the hydrophobic matrix.

A Trial was planned with Polyethylene 6000 to study the effect of a pore former. A pore former is responsible for the channel formation in the matrix, which in turn has impact on drug release from the drug product. Thus, the effect of addition of PEG was studied. **Table 4.29** shows the formula for the same.

Table 4.29 Formula for Trial 3

Sr. No	Ingredient	Quantity (%w/w)	Quantity (mg)	Role
1	Model Drug X	30	60	Active Ingredient
2	Hydrogenated castor oil	14	28	Hydrophobic Binder
3	PEG 6000	2	4	Pore Former
4	Lactose Monohydrate	53.5	107	Filler
5	Magnesium Stearate	0.5	1	Lubricant
Total Tablet Weight		100%	200 mg	

Procedure: Procedure followed was as same as given in δ4.7.1.1 Binder Screening Trials expect that PEG 6000 was also weighed and added in the FBD bowl before starting the granulation cycle.

Results:

1. **Impact of pore former on hydrophobic binder's melting property:**

   It is commonly observed that PEG impacts the melting points of the other excipients that are used with it. So, it was important to study the effect of presence of PEG on the hydrophobic binder's melting property. Thus, a study melting point study of Drug + PEG 6000 in ratio of 1:0.1 was carried out. The result was as follows-

Pure HCO melting point: 83 °C - 85 °C

HCO + PEG 6000 melting point: 78 °C - 79 °C

2. Flow Properties:

The flow properties evaluation was carried out as mention in δ4.7.1.1. The granules appearance for Trials with and without PEG 6000 are shown in **Fig 4.11.** The results from flow property evaluation is summarized in **Table 4.30**

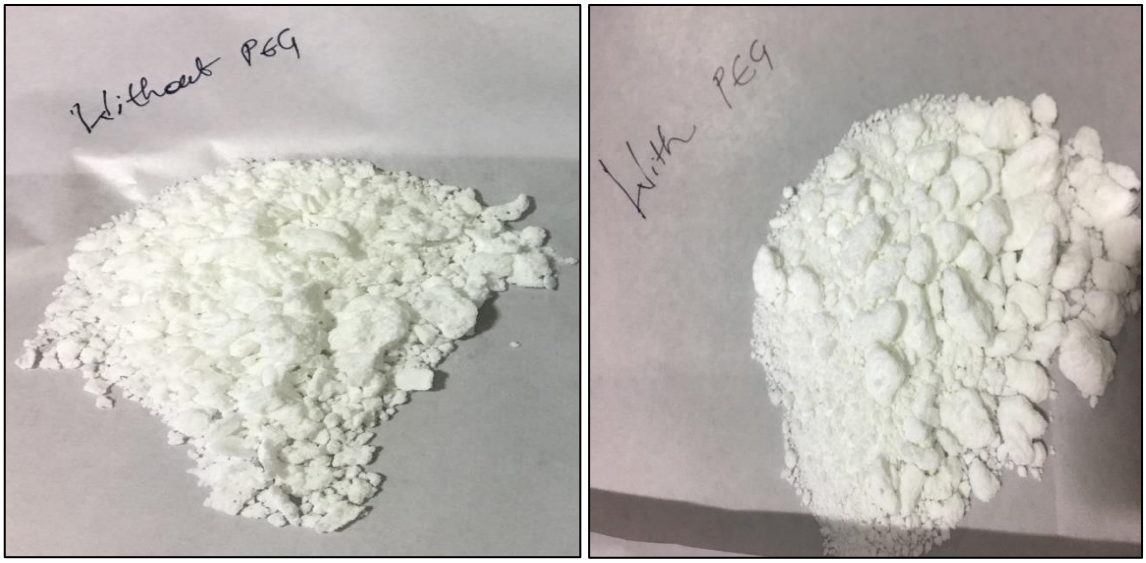


Fig 4.11 (a) Trial 1 without PEG 6000 **Fig 4.11 (b) Trial 3 with PEG 6000**

Fig 4.11 Granule Appearance for Trials with and without PEG 6000

Table 4.30 Flow Properties comparison for Trials with and without Pore Former

Parameter	Trial 1 (without PEG 6000)		Trial 3 (with PEG 6000)	
Bulk Density	0.51	-	0.44	-
Tapped Density	0.60	-	0.51	-
Compressibility Index	15.5	Fair to Good	14.86	Good
Hausner's Ratio	1.18	Good	1.17	Good

Discussion: The compressibility index for Trial 1 was found to be 15.5 which falls between the Fair and Good Flow specification of the USP Powder Flow. But, when PEG 6000 is added to the formulation, the flow considerably increases to Good Flow as per the USP specifications.

3. Weight Variation

10 tablets were randomly selected from the batch and a weight variation test was carried out. The results are shown in **Table 4.31:**

Table 4.31 Weight Variation test for Trials with and without PEG 6000

Parameter	Trial 3 (with PEG 6000)	Trial 1 (without PEG 6000)
Average Weight	201.03 mg	200.02 mg
SD	0.97	1.46 mg
RSD	0.48%	0.73%
Min	200.0 mg	198.0 mg
Max	202.6 mg	203.2 mg

4. Drug Release profile:

The dissolution study was performed as mention in δ4.4. The results of the same are shown in **Table 4.32**

Table 4.32 Dissolution Profile comparison for Trials with and without Pore Former

Batch #	Trial 1 without PEG 6000		Trial 3 with PEG 6000	
Time Points (hr)	**% Drug Release**	**% RSD**	**% Drug Release**	**% RSD**
0.5	30.8	0.6	39.7	2.2
1	34.6	2.3	53.1	1.6
2	41.1	1.8	70.2	2.3
3	49.7	2.4	81.6	0.6
4	56.3	2.1	88.5	0.9
5	**62.3**	**0.7**	**93.8**	**0.4**

Discussion: PEG 6000 was added to induce pore formation in the matrix of the tablet so as to facilitate the release of the drug. After the addition of pore former, the release increased to 97.4% as opposed to 62.3% without pore former after 5 hours (**Table 4.32**).

Conclusion from preliminary trials to study the effect of pore forming agent:

It was observed that the melting point of the meltable binder reduces in presence of PEG 6000. This reduction in melting point might be helpful since it gives a scope for reducing the processing temperature during granulation in FBD.

The addition of PEG 6000, improved the flow further. The addition of PEG 6000 solved the problem of incomplete release that was observed when only HCO was used in the formulation. Thus, it was decided to use PEG 6000 for the final product development.

The weight variation test shows that the uniformity of dosage unit was maintained even after the addition of PEG 6000.

The optimization of the concentration of PEG 6000 and HCO was done using DOE.

4.7.1.3 Effect of Filler Type

Filler's hydrophilic or hydrophobic nature may impact granule properties, which could have impact on drug release properties from the drug product. Thus, a study was conducted to select the type of filler that gives the best result for the production of MR tablet for Drug X. **Table 4.33** shows the formula for the trial with different filler.

Table 4.33 Formula for Trials with different Filler

Sr. No	Ingredient	Quantity (%w/w)	Quantity (mg)			Role
			Trial 1	Trial 2	Trial 3	
1	Model Drug X	30	60	60	60	API
2	Hydrogenated castor oil	14	28	28	28	Binder
3	PEG 6000	2	4	4	4	Pore Former
4	FlowLac 100	53.5	107	-	-	Filler
	Avicel 102		-	107	-	
	Starch 1500		-	-	107	
5	Magnesium Stearate	0.5	1	1	1	Lubricant
Total Tablet Weight		100%	200 mg			

Procedure: Procedure followed was as same as given in δ4.7.1.1 Binder Screening Trials, expect that in all the batches had different fillers were used.

Results:

1. **Flow Properties:**

   The flow properties evaluation was carried out as mention in δ4.7.1.1. The results from flow property evaluation is summarized in **Table 4.34**

Table 4.34 Flow Property comparison for Trials with different Filler

Parameter	Trial 3		Trial 4		Trial 5	
Bulk Density	0.44	-	0.39	-	0.48	-

Parameter	Trial 3		Trial 4		Trial 5	
Tapped Density	0.51	-	0.53	-	0.57	-
Compressibility Index	14.86	Good	26.42	Poor	12.5	Good
Hausner's Ratio	1.17	Good	1.364	Poor	1.16	Good

Discussion: As discussed before, the flow properties of Trial 3 (Flow Lac 100) are found to be good. Similar good flow properties were obtained for Trial 5 where filler used was lactose monohydrate was replaced with Strach 1500. On the other hand, when Avicel pH 102 was used, the flow was found to be poor.

2. Particle Distribution:

Fig. 4.11 (a) and (b) show the granule appearance for the trial with filler Starch 1500 and Avicel 102 respectively. Particle size distribution analysis before the co-mill step was carried using Retsch Sieve Shaker. The analysis was done for 5 min using 100 gm of granule blend. **Table 4.35** shows the results of the same.

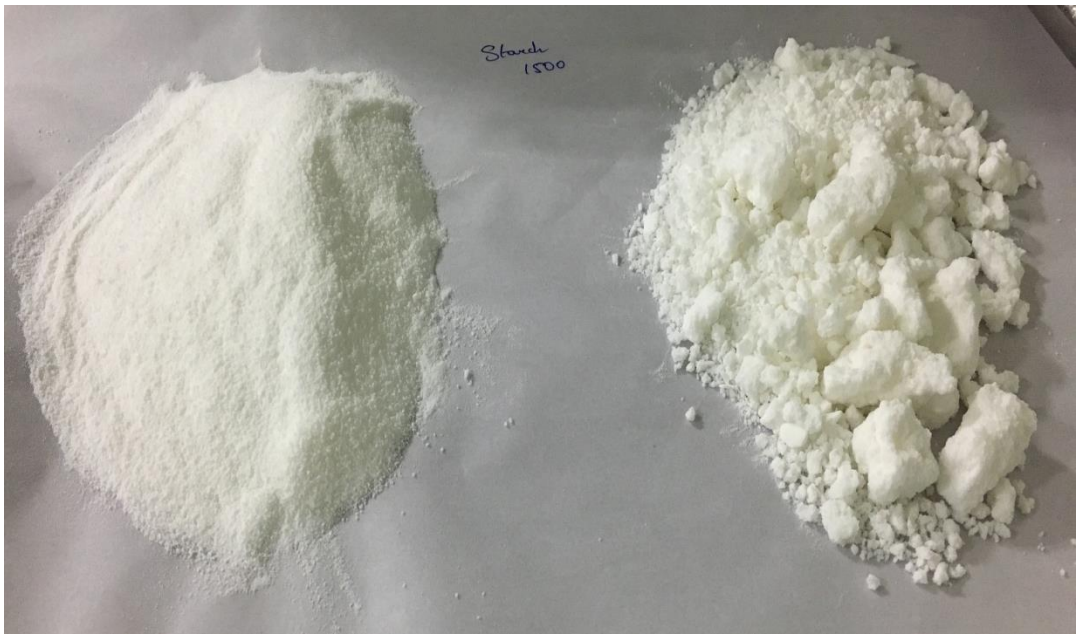


Fig. 4.11 (a) Granule Appearance for Trial with Starch 1500 as filler

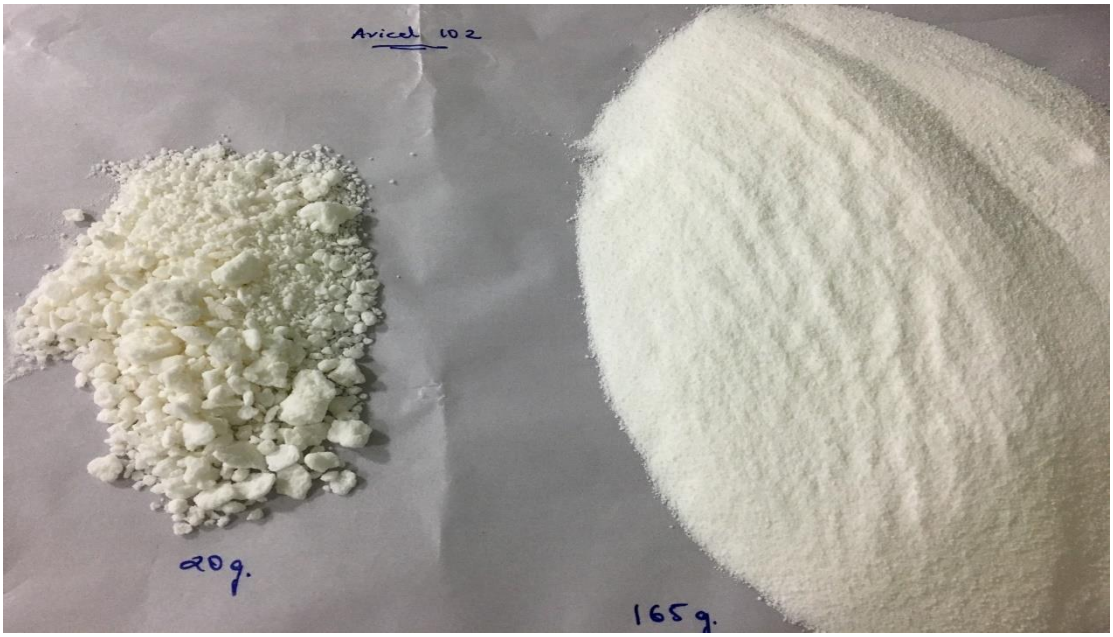


Fig. 4.11 (a) Granule Appearance for Trial with Avicel as filler

Table 4.35 PSD for Trials with different Filler

Parameter	Trial 3	Trial 4	Trial 5
30# passed & 60# retained	60%	25%	55%
60# passed	40%	75%	55%

Discussion: In Trial 4 (with Avicel pH 102 as the filler) it was observed that 75% of the partciles were 60# passed. Thus suggesting a higher ratio of fine to granules which may be due to insufficient granulation occuring when Avicel 102 is used as a filler. While, Flow Lac 100 and Strach 1500 showed comparable and optimum ratio of fines to granules.

3. Drug Release Profile:

The dissolution study was performed as mention in δ4.4. The results of the same are shown in **Table 4.36**

Table 4.36 Dissolution Profile for Trials with different Filler

Batch#	Trial 3		Trial 4	Trial 5
Time points (hrs)	**% Drug Release**	**% RSD**		
0.5	39.7	2.2	Non-compressible. Difficulty in achieve target weight.	With Starch as the filler, a hardness of more than 1.7Kp could not be achieved (fails friability).
1	53.1	1.6		
2	70.2	2.3		
3	81.6	0.6		
4	88.5	0.9		
5	93.8	0.4		

Discussion: During the compression of Trial batch 4 (Avicel pH 102 as filler), it was observed that a tablet weigh higher than 174 mg could not be achieved (required weight: 200 mg). Trial 5 with Starch 1500 could achieve the desired tablet weight but the tablets failed the friability test. The maximum hardness obtained was 1.7Kp. As opposed to this, the batch Flow Lac 100 was able to achieve the desired hardness as well as required tablet weight.

Conclusion from preliminary trials for effect of filler type:

Trial with Avicel pH 102 showed poor granulation and also while compression the blend could not achieve the required tablet weight. Thus, it can be concluded that Avicel could not be suitable for the preparation of the desired matrix tablets.

During compression of batch with Starch 1500, inability to achieve the desired hardness was observed. Due to low hardness, the tablets failed the friability test ad thus restricted its use in the preparation of the MR tablets for Drug X.

Thus, Flow Lac 100 was decided to be used as the filler should be considered for further batches.

4.7.2 Preliminary Trials for Process Variables

Based on the initial risk assessment it can be concluded that Granulation time, Fluidization Air Temperature and Milling Screen Size are the process variables that have a potential high impact on the CQAs. Thus, a one factor at a time (OFAT) approach was used to optimize these variables.

4.7.2.1 Granulation Time Optimization

Granulation time directly impacts the interaction time between meltable binder and API, thus affecting the coating of the binder on the API particles which in turn has an effect on the dissolution profile. Hence, granulation has a high potential to influence the performance of the final product. A trial to optimize the granulation time to obtained granules of desired properties was conducted and the formula for the same is mention in **Table 4.37**.

Table 4.37 Formula for Trial for Granulation time optimization

Sr. No	Ingredient	Quantity (%w/w)	Quantity (mg)	Role
1	Model Drug X	30	60	Active Ingredient
2	Hydrogenated castor oil	14	28	Hydrophobic Binder
3	PEG 6000	2	4	Pore Former
4	FlowLac 100	53.5	107	Filler
5	Magnesium Stearate	0.5	1	Lubricant
Total Tablet Weight		100%	200 mg	

Procedure for granulation:

1. All ingredients (except Magnesium Stearate) were weighed accurately and Sifted through 30#.
2. Weighed ingredients were transferred in a FBD bowl.
3. Dry mixing of the blend was done in FBD at minimum fluidization (10 CFM) for 30 sec.
4. After 30 secs, the temperature was increased to 10ºC above the melting point of meltable binder (maintaining the fluidization at minimum value)

5. Granulation was performed for the specified time (2, 4, 6, 10, 12min)
6. Once granulation is done, the temperature was reduced to room temperature for cooling. (fluidization at 40-50 CFM)
7. The material was removed from FBD and granules were sifted through 20#.
8. The 20# retained granules were co-milled and mixed with the remaining blend.
9. The blend was lubricated with 0.5% Magnesium Stearate (40# passed) in Turbula Blender.
10. The blend was compressed using Korsch XL

Procedure for strength analysis:

1. A sample of 1 gram from each granulated batch was taken.
2. The samples were placed on the stage in the die cavity maintaining the height up to 1mm.
3. **Fig. 4.13** shows the probe used for the crushing strength analysis.
4. Distance variable method was applied to determine the load required to crush the granules (Crushing Strength).

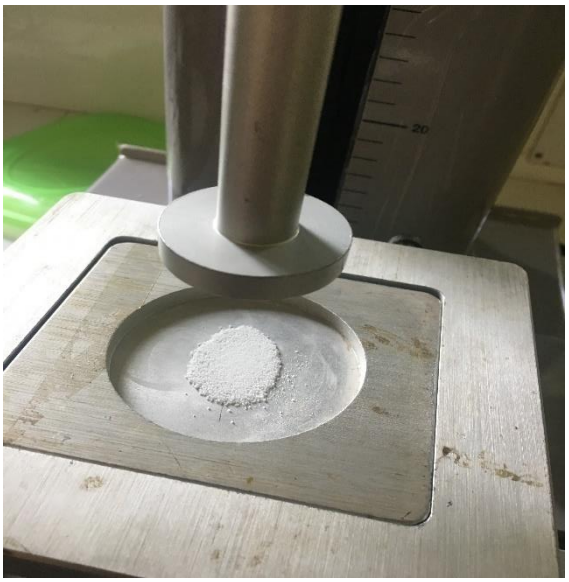


Fig.4.13 Texture Analyzer Probe used for Crushing Strength measurement

Result:

1. **Granule Crushing Strength**

   Using the data obtained from Texture analyzer, a graph of Mean Crushing strength (N) v/s Granulation Time (min) was plotted (**Fig. 4.14**)

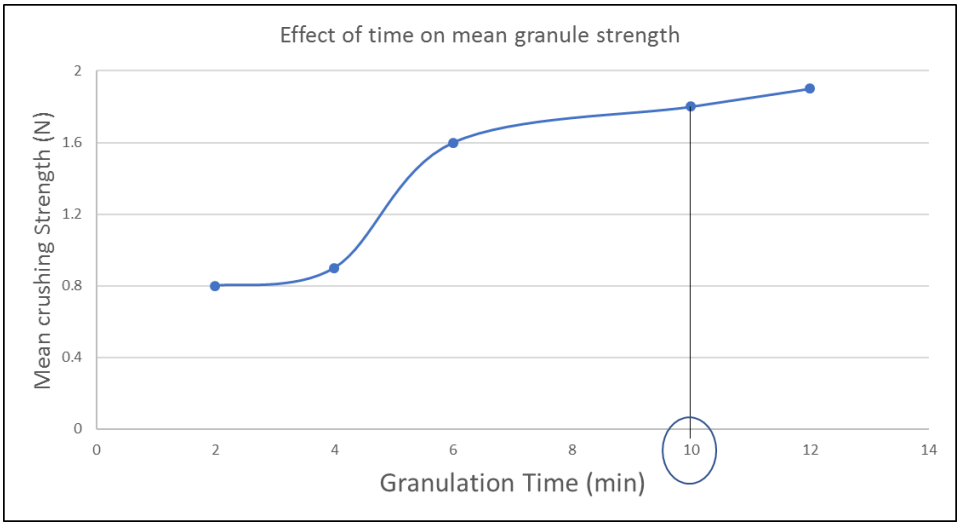


Fig. 4.14 Curve of Mean Crushing Strength versus Granulation Time

Discussion: From the graph, a steep rise (0.8N – 1.6N) is observed in the mean crushing strength from 2 min to 6 min. This steep rise is followed by a relatively constant phase (1.6N – 2N) from 6 min to 12 min with no major change in the mean crushing strength.

2. **Particle Size Distribution**

   Particle size distribution analysis before the co-mill step was carried using Retsch Sieve Shaker. The analysis was done for 5 min using 100 gm of granule blend. **Table 4.38** shows the results of the same.

Table 4.38 PSD for Trials with different Granulation Time

Parameter	Trial 6 (2 min)	Trial 7 (4 min)	Trial 8 (6 min)	Trial 9 (10 min)	Trial 10 (12 min)
30# passed & 60# retained	19%	27%	51%	61%	60%
60# passed	81%	73%	49%	39%	40%

Discussion: In Trial 6 and Trial 7, it was observed that 81% and 73% respectively of the partciles were 60# passed. Thus suggesting a higher ratio of fine to granules which may be due to insufficient granulation time for the binder to wet all the particles. While Trial 8 showed 49% fine and Trial 9 & 10 showed 40% fines thus suggesting better granulation than Trial 6 & 7. Thus, only Trial 8, 9 & 10 were further compressed and evaluated.

3. **Dissolution Study**

The dissolution study was performed as mention in δ4.4. The results for the same are shown in **Table 4.39**

Table 4.39 Dissolution Profile for Trials with different Granulation Time

Batch #	Reference	Trial 8	Trial 9	Trial 10
Time Point (hrs)	**% Drug Release**	**% Drug Release**	**% Drug Release**	**% Drug Release**
0.5	39	51.3	36.2	37.5
1	52	68.9	51.3	52.4
2	69	76.5	69.9	70.4
3	80	89.1	79.2	81.1
4	87	95.8	87.7	89.6
5	92	100.2	92.9	93.8

Discussion: Trial 8 with 6 min granulation showed a faster release as compared to reference product. While Trial 9 & 10 showed higher similarity with the reference product. Since a similar release profile for test to reference is obtained as 10 min, there is no need for granulation to be carried out till 12min. Thus, the granulation time was fixed at 10 min for the further trials. Although 10 – 12 min can be used for granulation and thus this range will be given for control strategy of the product.

Conclusion from trial for Optimization of Granulation Time:

From the graph, it can be concluded that from 6 min to 12 min a relatively constant phase (1.6N – 2N) with no major change in the mean crushing strength is obtained. From this we can conclude that an optimum time of 10 min for granulation time can be selected.

4.7.2.2 Fluidization Air Velocity Selection

The selection of the fluidization air velocity is very critical since the air velocity affects the assay as well as the particle size distribution of the granules.

Thus, in order to avoid drug loss due to excessive fluidization, the air velocity at the initial granulation stage was set at the lowest 10 CFM. At this velocity, sufficient bed movement was produced for material interaction during granulation.

The air velocity during binder cooling cycle was set such that there is sufficient movement in the bed which was observed at 40-50 CFM. A higher air velocity can cause excessive particle attrition and can damage binder coat on the API.

All the Trials were conducted using these air velocity values.

4.7.2.3 Processing Temperature Optimization

The granulation temperature directly impacts the melting of the binder and it affects the coating of the binder on the API particles intern affecting the dissolution profile. Thus, a trial was performed to optimize the processing temperature.

Formula: same as δ4.7.2.1 Granulation time optimization

Procedure:

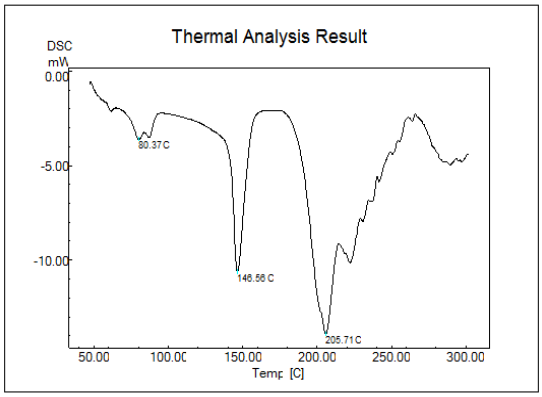
1. All ingredients (except Magnesium Stearate) mentioned in **Table 4.37** were weighed accurately and Sifted through 30#.
2. Weighed ingredients were transferred in a FBD bowl.
3. Dry mixing of the blend was done in FBD at minimum fluidization (10 CFM) for 30 sec.
4. After 30 secs, the temperature of FBD was increased to 10°C above the melting point of meltable binder (maintaining the fluidization at minimum value).
5. Granulation was performed at 3 different temperatures: 75°, 85°, 95°C
6. After the completion of granulation, the temperature of FBD was reduced to get the product to room temperature with maximum fluidization (fluidization at 40-50 CFM).
7. The material was removed from FBD and granules were sifted through 20#.
8. The 20# retained granules were co-milled and mixed with the remaining blend.
9. The blend was lubricated with 0.5% Magnesium Stearate (40# passed) in Turbula Blender.

Result:

1. **DSC Studies**

   DSC is a technique used to study the chemical changes in a substance when they are heated. These changes are important to understand the behavior of a substance when they are exposed to increased temperature. As the temperature is increased the sample eventually reaches its melting point and eventually may decompose. Since the FHMG process involves temperature application, it is important to study the behavior of the API when it is exposed to temperatures equal to and above the melting point. The DSC

curve for the physical mixture of the formulation and processed formulation blend are shown in **Fig. 4.13 and Fig. 4.14** respectively.



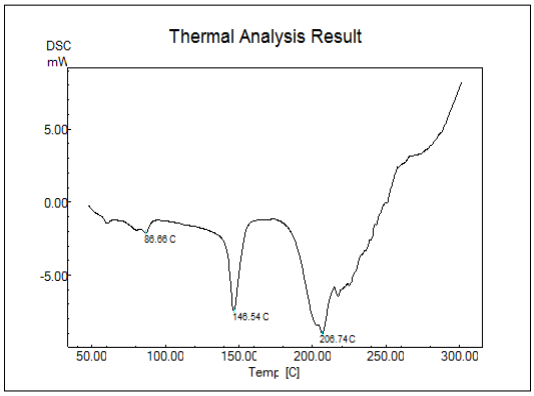


Fig.4.15 DSC curve for Unprocessed Physical Blend **Fig.4.16 DSC curve for Process Blend (@95°C)**

Discussion: Drug product DSC studies demonstrates that there is no shift in the melting point even after the it is exposed to 95°C (**Fig. 4.15 and Fig. 4.16)**. No alteration in the DSC i.e. no added is peak is observed which suggest no degradation or no generation of a degraded product. Thus, we can conclude that the drug is stable at a process temperature of 95°C.

2. Dissolution Profile

The dissolution study was performed as mention in δ4.4. The results of the same are shown in **Table 4.40**

Table 4.40 Dissolution Profile for Trial at Different Processing Temperatures

Batch#	Reference	Trial 11 @ 75°C	Trial 12 @ 85°C	Trial 3 @ 95°C
Time points (hr)	**% Drug Release**	**% Drug Release**	**% Drug Release**	**% Drug Release**
0.5	39	47	38	39
1	52	63	53	53
2	69	81	75	70
3	80	93	85	81
4	87	99	93	88
5	92	101	97	93
F2	-	**47**	**64.18**	**93.62**

Discussion: The melting point of the meltable binder is 83°-85°C. The effect of temperature was studied at 3 condition namely, at melting point (Trial 7), at 10°C lesser than the melting point (Trial 6), 10°C higher than the melting point of the meltable binder (Trial 3).

Trial 6 shows the least similarity with the reference product (F2 value: 47) followed by trial 7 with 85°C which has an F2 value of 64.18. Trial 3 was found to have the closest F2 value (93.6).

The lower F2 values of the Trial 6 and Trial 7 may be due to the insufficient melting of the binder which resulted in improper wetting and thus coating of the API by the binder. The inadequate coating the of drug can be extrapolated from the dissolution profile is faster than the reference product as well as the Trial 3. In Trial 3, the temperature was well above the melting point of the binder thus allowing proper wetting of the solid bed and thus a better coating and comparable drug release with the reference product.

Conclusion from trials for Optimization of Processing Temperature:

From the dissolution results, it is clear that a temperature 10°C above the melting point of the meltable binder is the minimum requirement for complete melting of the binder and properly coat the API so as to control the release of the drug from the hydrophobic matrix.

There is no degradation of the API or other excipient is observed in the DSC analysis at this temperature thus it can safely be used for the process of melt granulation.

Hence, 95°C was finalized as the process temperature for the final product formulation.

4.7.2.4 Selection of Milling Screen Size

PSD of the granules present in the end formulation determine the surface area for drug release. Milling has an impact on this PSD. But in a matrix tablet, PSD of the granules do not have a major impact the release profile. But a trial to ensure that there is no effect of the milling screen size was performed.

Formula: same as δ4.7.2.1 Granulation time optimization

Procedure: same as δ4.7.2.1 with granulation time as 10min and granulation temperature as 95°C. The milling was done with 0.8mm and 0.1mm screen

Result:

The dissolution study for the two batches with different milling screen size formulations were performed as mention in δ4.4. The results of the same are shown in **Table 4.41**

Table 4.41 Dissolution Profile for Trial with different Milling Screen Size

Batch#	Reference	Trial 13 (0.8mm screen)		Trial 14 (0.1 mm screen)	
Time points (hr)	% Drug Release	% Drug Release	%RSD	% Drug Release	%RSD
0.5	39	40.2	1.5	37.0	1.4
1	52	56.9	1.9	53.2	2.0
2	69	76.2	0.9	72.4	1.2
3	80	89.5	2.1	81.1	1.9
4	87	91.2	1.8	89.8	2.4
5	92	96	0.5	94.1	0.3

Result & Discussion: T test performed on the two milling screens 0.8mm and 0.1mm dissolution results. With $t(10) = 3.62$, $p<0.05$ showed a significant difference between the release pattern, a little fast release of drug from Trial 8 was observed. This may be due to reduced particle size of the granules which increases the exposed surface area for drug release thus resulting in relatively faster release. T test for 0.1 mm and Reference Product showed no

significant difference with t (10) = 2.372, $p<0.05$. Since the Trial 9 results were similar to the reference product, so 0.1mm was selected as the screen for the final product development.

4.7.2.5 Hardness Profiling

Tablet hardness or its breaking strength is an important and widely used parameter to control the manufacturing process. in many cases, it is used as a surrogate for compression force during manufacturing. It is very important to test this parameter because compression directly affects the tablet properties like disintegration, dissolution and friability. Thus, the hardness profile was carried out by collecting sample of different hardness and to the effect of the hardness of dissolution profile of the tablet was studied.

Formula: same as δ4.7.2.1 Granulation time optimization

Procedure: Blend preparation was done same as in δ4.6.2.3. Compression was carried out on Korsch XL and samples of different hardness were collected.

Result:

1. **Weight Variation:** 10 tablets were randomly selected from the batches and a weight variation test was carried out. The results are shown in **Table 4.42.**

Table 4.42 Weight Variation test for Trials at different hardness

Parameter	Trial 15 (@ Low Hardness)	Trial 16 (@ High Hardness)
Average Weight	199.93 mg	199.6 mg
SD	0.62	1.97 mg
RSD	0.31%	0.99%
Min	199.0 mg	194.3 mg
Max	200.0 mg	200.9 mg

2. **Dissolution Study:** The dissolution study for the two batches with different hardness were performed as mention in δ4.4. The results of the same are shown in **Table 4.43**

Table 4.43 Dissolution Profile for Trials with Different Tablet Hardness

Batch#	Trial 15 @ Low Hardness		Trial 16 @ High Hardness	
Time points (hr)	% Drug Release	%RSD	% Drug Release	%RSD
0.5	39	0.6	38	1.2
1	53	2.2	54	2.3
2	70	1.8	70	1.5
3	81	2.1	80	2.4
4	88	2.1	89	1.8
5	93	0.9	93	0.7

Discussion: The hardness profiling was done as low hardness of 4.0 Kp – 5.5 Kp and high hardness of 5.5 Kp – 7.0 Kp. A paired T Test was performed on the hardness sample's dissolution profile {$t(10) = 0, p<0.05$}. The drug release from both the hardness was found to be equivalent with no much difference.

Conclusion from trials for Hardness profiling:

Since the drug release was found to be independent of the tablet hardness, a hardness of 4.5 Kp – 6.0 Kp was chosen for the final product. The hardness was selected in a way that it is optimum for both final product performance and easy processing. A lower hardness may lead to failing of tablet in friability test and a very high hardness may show capping during compression.

4.8 Optimization using Design of Experiment: 3^2 Full Factorial

4.8.1 Justification for selection of factors and responses

From the trials taken and from the update risk assessment, we can conclude that **concentration of meltable binder and pore former play an important factor in influencing the dissolution profile of drug product.**

- Concentration of meltable binder: Hydrophobic Binder concentration may impact granule properties and tablet disintegration, which have an impact on drug release properties from the drug product.
- Concentration of pore former: Pore former is responsible for the channel formation in the matrix, which in turn has impact on dissolution profile of the drug product.

4.8.2 Objective of DoE trials

1. A DoE conducted with factors that have a high risk of impacting the formulation.
2. The nature and degree of impact of factors on response is evaluated with DoE.
3. A design space is created using DoE. When working within this space, the formulation is expected to possess the desired pre-determined QTPPs.

4.8.3 Composition & design matrix of 3^2 full factorial design

The optimization study was done using Design Expert® Software v. 10.0. The levels chosen for variable for the 3^2 full factorial design are mention in **Table 4.44** and the responses measured are as follows:

R1: Drug Release after 2 hours

R2: Drug Release after 5 hours

Table 4.45 shows the 3^2 full factorial design matrix with two extra batches shown Batch No. 10* and 11*. Apart from the 9 DoE runs, these are extra center point batches were performed which act at replicate batches to estimate the reproducibility and variability.

Table 4.44 Levels of variables in 3^2 full factorial design (Actual and Coded Values)

Hydrophobic Binder Concentration		Pore former Concentration
Actual Value (mg/tablet)	Coded Value	Actual Value (mg/tablet)
18.0	-1	0.50
28.0	0	2.25
38.0	+1	4.00

Table 4.45 3^2 full factorial design matrixes

Batch No.	Order of Batch Preparation	Conc of HCO		Conc of PEG 6000	
		Coded	Actual (mg/tab)	Coded	Actual (mg/tab)
1	1	-1	18	-1	0.50
2	4	0	28	-1	0.50
3	11	1	38	-1	0.50
4	8	-1	18	0	2.25
5	2	0	28	0	2.25
6	5	1	38	0	2.25
7	10	-1	18	1	4.00
8	3	0	28	1	4.00
9	6	1	38	1	4.00
10*	9	0	28	0	2.25
11*	7	0	28	0	2.25

4.8.4 Result:

The response value, obtained after the preparation and evaluation of the 11 DoE batches, were analyzed using Design Expert® Software v. 10.0. The response values obtained for different DoE batches are mentioned in **Table 4.46**. The statistical significance of the variables (R1 and R2) is established with ANOVA by Design Expert® Software using the response value data. The graphical representations given by the Software were used to study the impact of each factor on the desired outcome. The software not only determine the main effect of each factor but also studies interactions between the factors.

Table 4.46 Design Matrix with Response values R1 and R2

Batch No.	Conc of HCO	Conc of PEG 4000	R1 (%)	R2 (%)
1	-1	-1	**67.2**	**96.8**
2	0	-1	**66.1**	**96.3**
3	1	-1	**50.5**	**70.9**
4	-1	0	**65.3**	**91.2**
5	0	0	**64.1**	**94.0**
6	1	0	**50.9**	**80.7**
7	-1	1	**68.1**	**98.5**
8	0	1	**61.0**	**93.1**
9	1	1	**48.8**	**79.8**
10*	0	0	**63.6**	**93.8**
11*	0	0	**63.9**	**94.1**

4.8.4.1 Interpretation & Analysis of Response for Response R1[51]

Table 4.47 and **Table 4.48** show the statistical data generated by Design Expert® Software using the response value of R1 and R2 for different batches. The correlation coefficient R square value was found to be 0.9769 indicated good fit of the linear equation. All of the responses showed a nonsignificant lack of fit ($p > 0.1$), showing the adequacy of the model fit when fitted in the linear equation model. From the results of ANOVA, p value was found to be less than 0.05 indicated that the factors have a significant effect on the response R1.

Table 4.47 Summary of regression analysis for Response R1 (Drug Release at 2 hr)

R^2	0.9769
Adjusted R^2	0.9538
Standard Deviation	1.5500
Mean	60.85

Table 4.48 ANOVA of response R1 (Drug Release at 2 hr)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	505.39	5	101.08	42.28	0.0004	significant
A-A	423.36	1	423.36	177.10	< 0.0001	
B-B	5.61	1	5.61	2.35	0.1862	
AB	1.69	1	1.69	0.71	0.4388	
A^2	70.32	1	70.32	29.41	0.0029	
B^2	0.044	1	0.044	0.018	0.8975	
Residual	11.95	5	2.39			
Cor Total	517.35	10				

The Design Expert® Software gives an equation with which one can calculate the response that will be produce using for a particle value of variable. The **Final Equation in Terms of Coded Factors for Drug Release at 2hours is:**

$R1 = +63.64737 – 8.40*A – 0.9667*B – 0.650*AB – 5.268*A^2 + 0.13158*B^2$…… Eq (1)

The linear equation (1) generated after the statistical analysis exemplifies the quantitative effect of factors or independent variables (A) & (B) on the response R1 i.e. drug release at 2 hours. The coefficients of the factors in the equation reflect the importance of that particular factor. The coefficients associated with more than one factor reflect the interaction among those factors.

The Response Surface plots, contour plot and 3D response surface plot as shown in **Fig. 4.17(a) and Fig. 4.15(b)** respectively, were also obtained from Design Expert® Software on the basis of equation generated to estimate and understand the effect of the independent variables on the drug release from the matrix tablet.

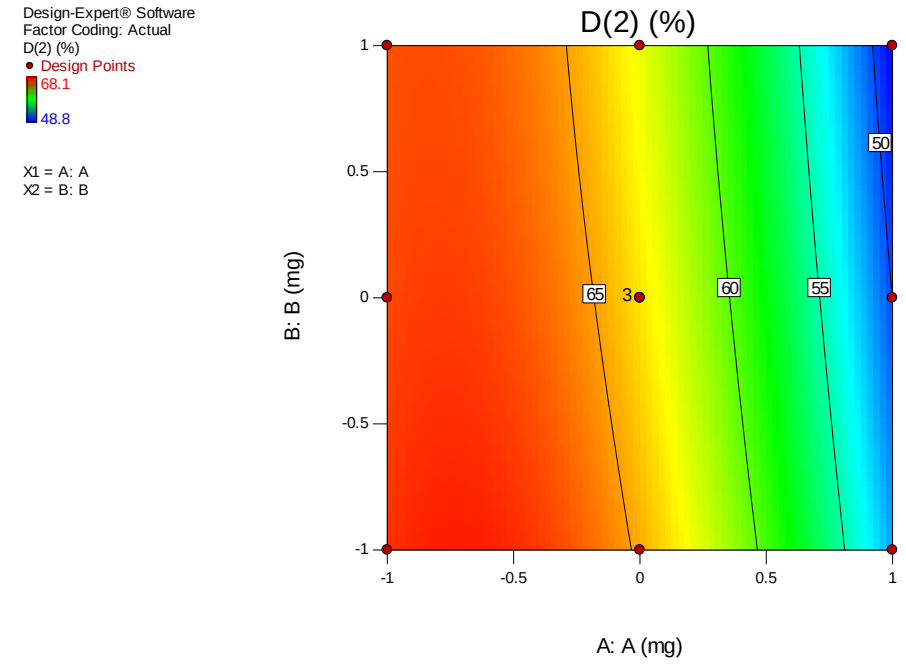


Fig. 4.17 (a)

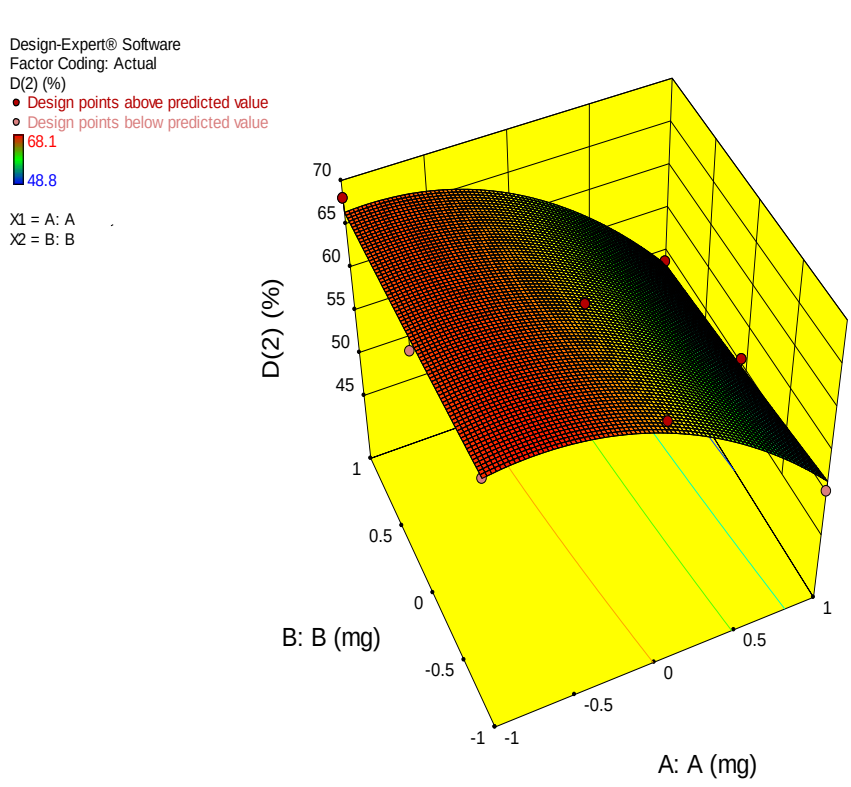


Fig. 4.17 (b)

Fig. 4.17 Response surface graphs (a) Contour plot (b) 3-D plot for Drug Release at 2 hours

Conclusion from statistical interpretation for Response R1:

From the linear equation (1) and Response Surface plots **Fig. 4.17**, it can be concluded that the both Factors A and B showed negative effect on drug release at 2 hours. That is, an increase in the concentration of any one or both will lead to slower drug release from the formulation. The major negative effect of Factor A (Concentration of hydrophobic meltable binder) on drug release could be due to insufficient of wetting of the tablet matrix which could be caused due to the hydrophobic nature of the binder and hence reduces drug release. Value of coefficient of interaction between the factor A and B, and of Factor B show that they do not have a significant effect on drug release at 2 hours.

4.8.4.2 Interpretation & Analysis of Response for Response R2

Table 4.49 and **Table 4.50** show the statistical data generated by Design Expert® Software using the response value of R1 and R2 for different batches. The correlation coefficient R square value was found to be 0.9074 indicated good fit of the linear equation. All of the responses showed a nonsignificant lack of fit (p> 0.1), showing the adequacy of the model fit when fitted in the linear equation model. From the results of ANOVA, p value was found to be less than 0.05 indicated that the factors have a significant effect on the response R2.

Table 4.49 Summary of regression analysis for Response R2 (Drug Release at 5 hr)

R-Squared	0.9074
Adj R-Squared	0.8148
Standard Deviation	3.77
Mean	89.87

Table 4.50 ANOVA of response R2 (Drug Release at 5 hr)

Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**	
Model	695.88	5	139.18	9.80	0.0128	significant
A-A	502.34	1	502.34	35.37	0.0019	
B-B	9.63	1	9.63	0.68	0.4478	
AB	12.96	1	12.96	0.91	0.3833	
A^2	164.38	1	164.38	11.57	0.0192	
B^2	0.90	1	0.90	0.063	0.8117	
Residual	71.02	5	14.20			
Cor Total	766.90	10				

The Design Expert® Software gives an equation with which one can calculate the response that will be produce using for a particle value of variable. The **Final Equation in Terms of Coded Factors for Drug Release at 5hours is:**

$D_{5hr} = +93.94211 - 9.15*A + 1.26667*B + 1.800*AB - 8.05526*A^2 + 0.59474*B^2$…. Eq(2)

The Response Surface plots (contour plot and 3D response surface plot) as shown in **Fig. 4.18(a) and 4.18(b)** respectively were obtained from the software on the basis of equation generated to estimate and understand the effect of the independent variables on the drug release from the matrix tablet.

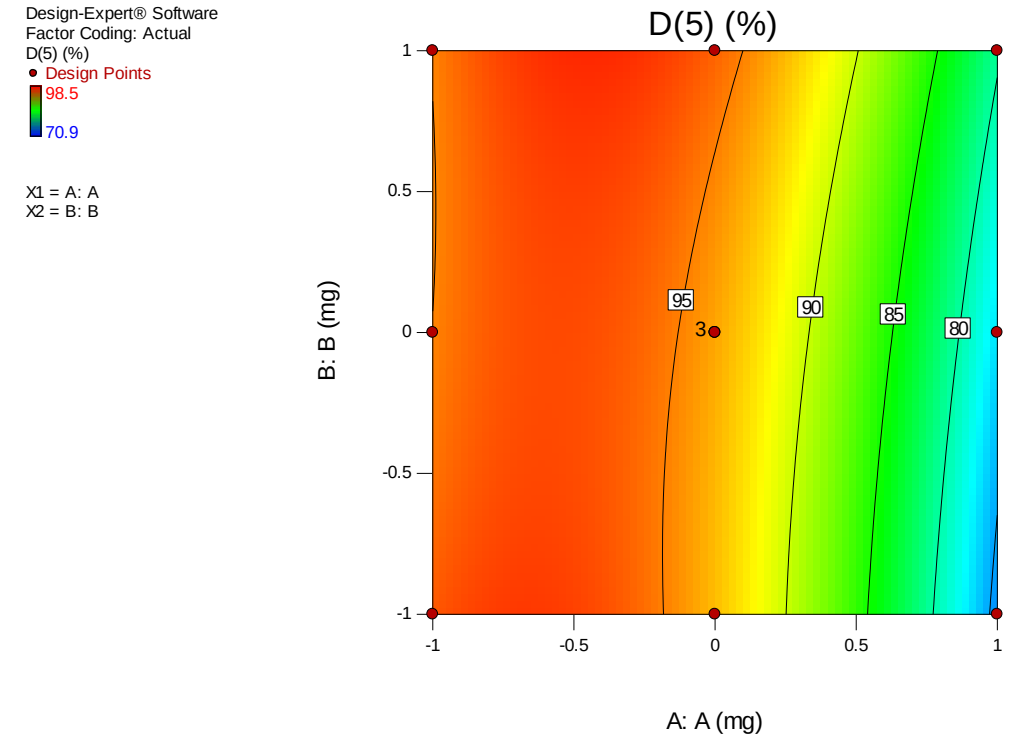


Fig. 4.18 (a)

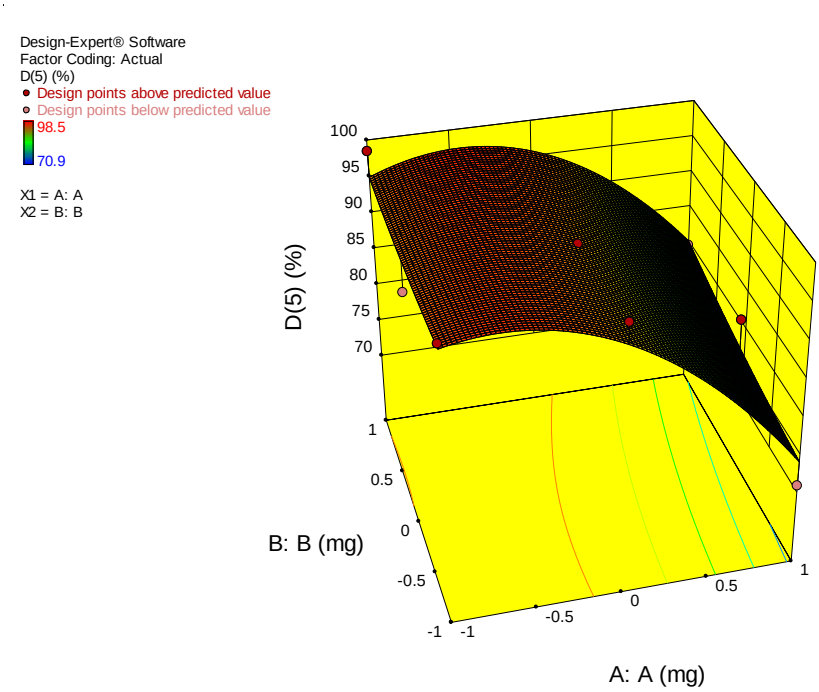


Fig. 4.18 (b)

Fig. 4.18 Response surface graphs (a) Contour plot (b) 3-D plot for Drug Release at 5 hours

Conclusion from statistical interpretation for Response R2:

From the linear equation (2) and Response Surface plots **Fig. 4.18**, it can be concluded that the Factors A showed negative effect while Factor B had a positive effect on drug release at 5 hours. That is, if the drug release is to be increased, the concentration of Factor A should be decreased while concentration of Factor B should be increased. The major negative effect of Factor A (Concentration of hydrophobic meltable binder) on drug release could be due to insufficient of wetting of the tablet matrix which can be attributed to the hydrophobic nature of the binder and hence reduces drug release. The positive co-efficient of Factor B shows a direct and linear relation between concertation of pore former on the drug release at 5hr. Value of coefficient of interaction between the factor A and B, and of Factor B show that they do not have a significant effect on drug release at 5 hours.

4.8.4.3 Design Space[52]

A design space is generated by overlaying all the contour plots obtained for different responses. The **Fig. 4.19** shows an overlay plot of the response factors within which is a yellow region called the design space.

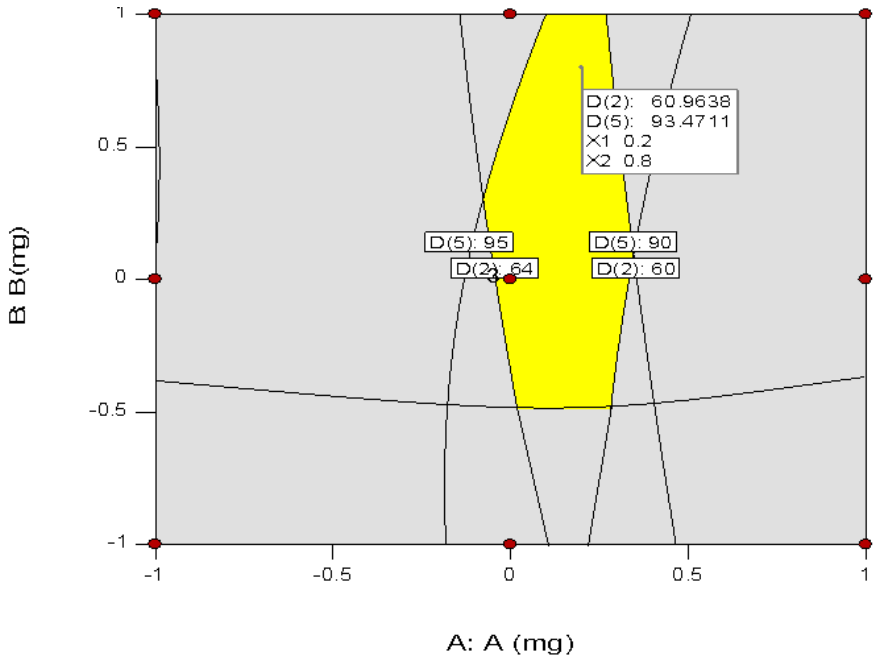


Fig. 4.19 Overlay Plot

Interpretation:

Yellow region in the overlay plot shows the acceptable region where in the formulation of batches will fulfil the criteria set as QTPP. That is, as long as the formulation variables are within the range represented by the design space, the product obtained will possess the desired quality, safety and efficacy attributes.

In order to validate the results from DOE, a check point batch with the predicted levels was prepared and evaluated. The concentration for the Binder and Pore former for the preparation of check point batch were obtained from the Design Space solution (Flagged in Fig. 4.19).

4.9 Check Point Batch

In order to validate the equation derived after applying DOE, a check point batch with the predicted levels was prepared and evaluated. (**Table 4.51**)

Table 4.51 Formula for Check point batch

Sr. No	Ingredient	Coded Value (from design Space)	Quantity (%w/w)	Quantity (mg)	Role
1	Model Drug X	-	30	60	API
2	Hydrogenated castor oil	0.2	15	30	Binder
3	PEG 6000	0.8	3.65	1.83	Pore Former
4	FlowLac 100	-	52.67	105.35	Filler
5	Magnesium Stearate	-	0.5	1	Lubricant
Total Tablet Weight			100%	200 mg	

Procedure:

1. All ingredients (except Magnesium Stearate) were weighed accurately and Sifted through 30#.
   - Weighed ingredients were transferred in a FBD bowl.
2. Dry mixing of the blend was done in FBD at minimum fluidization (10 CFM) for 30 sec.
   - After 30secs, the temperature was increased to 95ºC while maintaining the fluidization at minimum value for 10min
3. After the completion of granulation, the temperature of FBD was reduced to get the product to room temperature with maximum fluidization (fluidization at 40-50 CFM).
   - The material was removed from FBD and granules were sifted through 20#.
4. The 20# retained granules were co-milled and mixed with the remaining blend.
   - The blend was lubricated with 0.5% Magnesium Stearate (40# passed) and compression was carried out on Korsch XL.

Fig. 4.20 Final Optimized Procedure for MR tablets of Drug X

Results:

1. **Flow Data**

   Flow properties of the powders were tested using Tap density tester (TD 1025) by Labindia. The USP method I - graduated cylinder was followed i.e. 500 taps and 750 taps with 50 gm of granule blend. The **Table 4.52** shows the flow properties obtained for checkpoint batch.

Table 4.52 Flow Properties evaluation for Check Point Batch

Parameter	Observed Value	Interpretation
Bulk Density (g/ml)	0.4900	-
Tapped Density (g/ml)	0.5599	-
CI %	13.50	Good Flow
HR	1.1428	Good Flow
FFC	7.5	Good Flow

2. **Tablet Compression**

   Tablet Compression was carried out at parameters mentioned in **Table 4.26** of δ4.7.1.1. The tableting operation was performed using Korsch XL and was found to be smooth with no major issues and minimum variation in the product during the compression. The results from evaluation of tablets from check point are mentioned in **Table 4.53.**

Table 4.53 Evaluation of Tablets from Check Point Batch

Average Weight	200.02 mg
SD	0.61 mg
RSD	0.31%
Min	199.2 mg
Max	201.3 mg
Hardness	5 ± 1 Kp
Thickness	4.27 ± 0.04 mm
Diameter	7.9 ± 0.01mm

3. **Dissolution Data**

The dissolution study carried for the checkpoint batch was same as that of the Reference product, the parameters of which are mention in **Table 4.9** of δ4.4**.** The dissolution profile comparison of Reference product and Checkpoint batch is shown in **Fig. 4.21.**

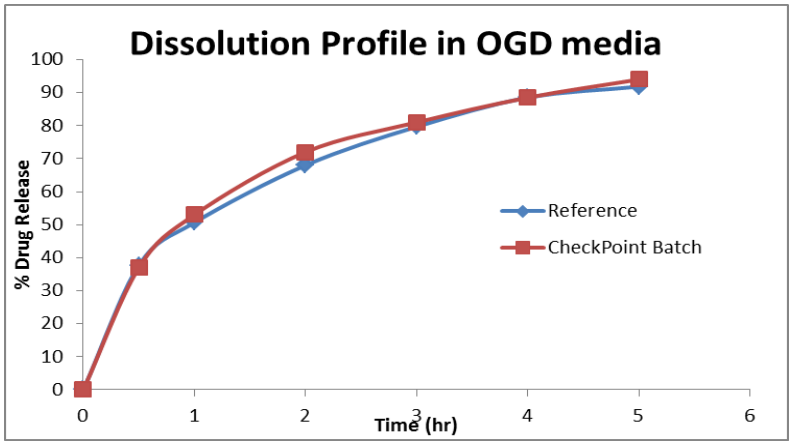


Fig. 4.21 Drug Release Profile of Checkpoint Batch in OGD Media

Discussion: The predicted value from the software and the practically obtained value for R1 (Drug release at 2 hours) and R2 (Drug release at 5 hours) were close (**Table 4.54, Fig. 4.21**) thus successfully validating the model obtained from the Design Expert software. Also, the dissolution profile of the checkpoint batch was found to be comparable to the Reference product since the **F2 value** obtained was **77.75** and **F1 value** was **3.02.**

Table 4.54 Comparison for Predicted and Practical Values

Parameter	Predicted Value	Practical Value
Drug Release at 2hr (R1)	60.9638 %	61.8% ± 0.3 %
Drug Release at 5hr (Rs)	93.4711 %	94.9% ± 1.2 %

Order of Drug Release: Annexure 1 shows the calculation for release order. It is evident that the formulation follows a Higuchi plot since the R^2 is found to be 0.988.

4. **Multi Media Dissolution of Check Point Batch**

The **Fig. 4.22 (a) to 4.22 (c)** and **Table 4.55 (a) to 4.55 (c)** shows the multi-media study for the test product in comparison to the reference product. The dissolution study of the checkpoint batch and reference product show a similar drug release profile.

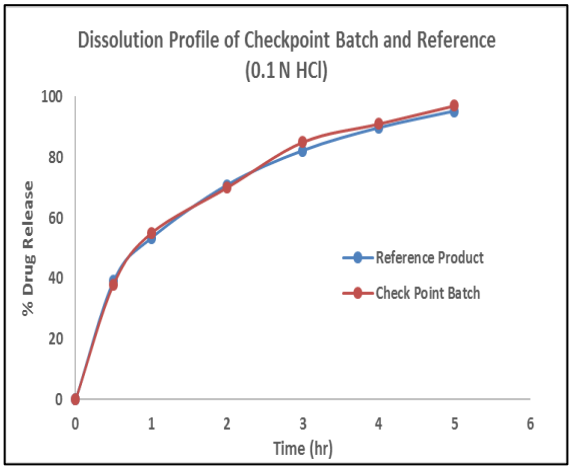


Fig. 4.22 (a) Dissolution Profile comparison in 0.1N HCl

Table 4.55 (a) Dissolution Profile comparison in 0.1N HCl

Time points	Reference	Checkpoint Batch
0.5	39	38
1	53	55
2	71	70
3	82	85
4	90	91
5	95	97

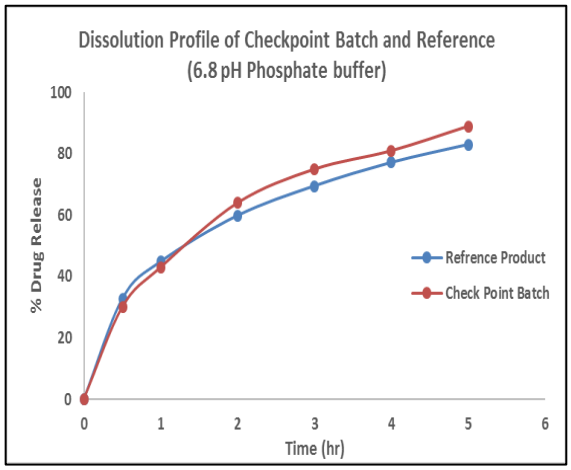


Fig. 4.22 (a) Dissolution Profile comparison in 6.8 pH Phosphate buffer

Table 4.55 (b) Dissolution Profile comparison in 6.8 pH Phosphate buffer

Time points	Reference	Checkpoint Batch
0	0	0
0.5	33	30
1	45	43
2	60	64
3	70	75
4	77	81
5	83	89

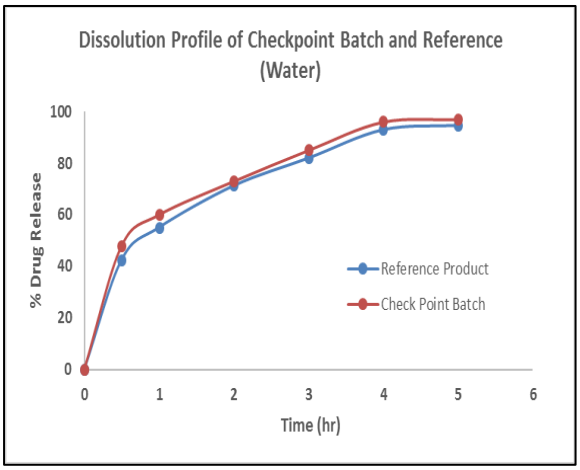


Fig. 4.22 (c) Dissolution Profile comparison in Water

Table 4.55 (c) Dissolution Profile comparison in Water

Time points	Reference	Checkpoint Batch
0	0	0
0.5	43	48
1	55	60
2	71	73
3	82	85
4	93	96
5	95	97

Conclusion from Check Point Batch Trials: The results of check point batch were found to be comparable to the predicted values derived from the linear equation. Hence, the design & statistical models are mathematically valid and one can reach to an optimized point in shortest time with minimum efforts by adopting organized formulation approach.

4.10 Update Risk Assessments

4.10.1 Drug substance attributes

After the preliminary OVAT trials, the risk assessment of Drug substance has been updated in **Table 4.56** and justification for the same is given in **Table 4.57**

Table 4.56 Update Risk Assessment of Drug substance attributes

Drug Substance Attributes	Drug Product CQAs		
	Assay	Uniformity of Dosage Unit	Dissolution
Solid State Form	Low	Low	Low*
Particle Size Distribution	Low*	Low*	Low*
Flow Properties	Low	Low	Low
Hygroscopicity	Low	Low	Low
Moisture Content	Low	Low	Low

Table 4.57 Justification for risk assessment of the drug substance attributes

Drug Substance Attributes	Drug products CQAs	Initial Risk	Updated Risk	Justification
Solid state Form	Dissolution	Medium	Low*	Different solid state forms of the drug substance could different solubility and can impact tablet dissolution. However, the DMF holder consistently provides the same crystalline form of drug with controlled PSD. In addition, Drug Product DSC studies demonstrates that crystalline form remains the same in the end

				formulation. Hence, it is unlikely to affect drug product dissolution.
PSD (Particle Size Distribution)	Assay	Medium	Low*	PSD may adversely impact the blend flowability which may cause inconsistency in assay and uniformity of the dosage unit. However, the development of the tablet is done by melt granulation process was adopted which has shown consistent results for assay and uniformity of dosage unit. Hence, the risk is reduced to low.
	Uniformity of Dosage Unit	Medium	Low*	
	Dissolution	Medium	Low*	The formulation with D90 NMT 87.69 µ particle size range exhibited dissolution similar to reference product. Therefore, drug substance PSD D90 NMT 87.69 µ was selected for development. Thus, the risk is reduced to low.

4.10.2 Formulation Variables

After the preliminary OVAT trials, the risk assessment of Formulation Variables has been updated in **Table 4.58** and justification for the same is given in **Table 4.59**

Table 4.58 Updated Risk Assessment of Formulation Variables

Formulation Variable	Drug Product CQAs		
	Assay	Uniformity of Dosage Unit	Dissolution
API	**Low***	**Low***	**Low***
Filler	**Low**	**Low**	**Low***

Hydrophobic Binder	**Low**	**Low***	**Low***
Pore Former	**Low**	**Low**	**Low***
Lubricant	**Low**	**Low**	**Low**

Table 4.59 Justification for the Updated Risk Assessment of the Formulation Variables

Formulation Variables	Drug Product CQAs	Initial Risk	Updated Risk	Justification
API	Assay	Medium	Low*	PSD may adversely impact the blend flowability which may cause inconsistency in assay and uniformity of the dosage unit. However, the development of the tablet is done by melt granulation process was adopted which has shown consistent results for assay and uniformity of dosage unit. Hence, the risk is reduced to low.
	Uniformity of Dosage Unit	Medium	Low*	
	Dissolution	Medium	Low*	The formulation with D_{90} NMT 87.69 µ particle size range exhibited dissolution similar to reference product. Therefore, drug substance PSD D90 NMT 87.69 µ was selected for development. Thus, the risk is reduced to low.
Filler	Dissolution	High	Low*	Flow Lac 100 is now fixed for the final product. It gives granules with desired flow, particle size and a dissolution

Formulation Variables	Drug Product CQAs	Initial Risk	Updated Risk	Justification
				profile comparable to the reference product.
Hydrophobic Binder	Uniformity of Dosage Unit	Medium	Low*	Concentration of hydrophobic binder affects particle size distribution of granules which is likely to affect the uniformity of drug product. The trials conducted at 15% binder shows uniformity of dosage unit which was analyzed by weight variation test.
	Dissolution	High	Low*	Hydrophobic Binder concentration may impact granule properties and tablet disintegration, which have an impact on drug release properties from the drug product. The concentration of binder is fixed to 14% to 16%. This range ensure drug release similar to reference Product
Pore Former	Dissolution	High	Low*	Pore former is responsible for the channel formation in the matrix, which in turn has impact on drug release from the drug product. The level of Pore former is fixed to 1.5% to 2%. This range ensure drug release similar to reference Product

4.10.3 Process Variables

After the preliminary OVAT trials, the risk assessment of Process Variables has been updated in **Table 4.60** and justification for the same is given in **Table 4.61**

Table 4.60 Updated Risk Assessment of Process Variables

Process Variable	Drug Product CQAs		
	Assay	Uniformity of Dosage Unit	Dissolution
Sifting	Low	Low	Low
Granulation: Time	Low	Low	Low*
Granulation: Fluidization Air Temperature	Low	Low	Low*
Granulation: Fluidization Air Velocity	Low*	Low*	Low
Milling	Low	Low	Low*
Blending & Lubrication	Low	Low	Low
Compression	Low*	Low*	Low*

Table 4.61 Justification for the Initial Risk Assessment of the Process Variables

Process Variables	Drug Product CQA's	Initial Risk	Updated Risk	Justification
Granulation: Time	Dissolution	High	Low*	Granulation time directly impacts the interaction time between meltable binder and API; The granulation time was optimized to 10min and the dissolution at this time matches the

Process Variables	Drug Product CQA's	Initial Risk	Updated Risk	Justification
				reference product. Thus, the risk is reduced to low.
Granulation: Fluidization Air Temperature	Dissolution	High	Low*	Since the granulation temperature directly impacts the melting of the binder, it affects the coating of the binder on the API particles and thus has an effect on the dissolution profile. The granulation temperature was optimized to 95°C and the dissolution at this time matches the reference product. Thus, the risk is reduced to low.
Granulation: Fluidization Air Velocity	Assay	Medium	Low*	At high air flow, assay of the product may reduce due to drug loss. So, the fluidization during granulation is maintained at minimum, 10CFM, to avoid excessive fluidization. Thus, the risk is reduced to low.
	Uniformity of Dosage Unit	Medium	Low*	A higher air velocity can cause excessive particle attrition and can damage binder coat on the API. So, the air velocity during cooling cycle was set such that there is sufficient movement in the bed which was observed at 40-50 CFM. Thus, the risk is reduced to low.
Milling	Dissolution	Medium	Low*	Milling has an impact on the PSD of the granules present in the end formulation

Process Variables	Drug Product CQA's	Initial Risk	Updated Risk	Justification
				which determine the surface area available for dissolution. The dissolution results of trial obtained will milling screen 0.1 mm match the drug release profile of reference product. Thus 0.1 mm screen is chosen for final product development. Hence the risk is reduced to low.
Compression	Assay	Medium	Low*	A faster than optimal press or suboptimal speed could likely result in die filling and weight variability which may impact tablet assay and CU. At a turret spend of 20 rpm, no weight variation was observed. Hence, at this speed, the risk is reduced to low.
	Uniformity of Dosage Unit	Medium	Low*	
	Dissolution	High	Low*	Hardness profile challenge was carried out. The dissolution profile was found to be independent of hardness of the tablet. Thus, the risk is reduced to low.

4.11 Control Strategy

ICH guideline defines control strategy as 'a strategic set of controls, derived from existing product and process understanding that guarantees process performance and product quality' That is, during product manufacturing if these set of controls are followed, the product thus obtained will be of the desired quality, safety and efficacy.

The **Table 4.62** shows Control strategy for Martials used for formulation of product and Process parameters. **Table 4.63** shows those parameters which are to be kept constant during the formulation manufacturing.

Table 4.62 Control Strategy for Material Attributes and Process Attributes

Factors	Attribute	Data obtained At	Proposed Range	Reason for Control
Model Drug X	Melting Point (°C)	212 - 213	212 - 217	Controlling these set of attributes ensures a consistent solid state form of drug (Crystalline)
Lactose Monohydrate	Amount	53%	49% - 54%	The Filler in this range ensures the required flow properties, compressibility and in-vitro profile. A change in this concentration may lead to change in granule properties thus causing variable between batches.
Hydrogenated Castor oil	Amount	15%	14% - 16%	The meltable binder in this range ensures the required in-vitro dissolution profile. A

Factors	Attribute	Data obtained At	Proposed Range	Reason for Control
				change in this concentration may lead to increase or decrease in the level of coating on the API and thus will impact the dissolution.
PEG 6000	Amount	1.8%	1.5% - 2%	The pore former in this range ensures the required in-vitro dissolution profile. A change in this concentration may lead to increase or decrease in number of channels formed and thus will impact the dissolution.
Granulation	Time (min)	10	10-12	This range is selected to obtain consist granule properties like the granule strength and flow properties
	Temperature (°C)	95	95-100	
Fluidization Air Velocity	During Granulation (CFM)	10	10 -15	This range is selected to obtain consist granule particle size distribution, flow properties.
	after granulation (CFM)	45	40-50	

Table 4.63 Constant Parameters for manufacturing of MR tablet of Drug X

Factors	Attributes	Data obtained At		Reason for Control
Model Drug X	PSD (µ)	D10	5	This PSD gives a comparable in-vitro dissolution with the reference product. A change in this PSD may alter the surface area of the particle and thus affect the dissolution rate.
		D50	26.11	
		D90	87.69	
Magnesium Stearate	Amount	0.5%		Lubricant at this level gives a consistent batch to batch results.
Co-mill	Screen Size	1.106 mm		This value guarantees consistency in PSD of the final blend
	Milling Speed	1000 rpm		
Lubrication	Time	3 min		This provided consistency from batch to batch
	Speed	25 rpm		
Compression	Turret Speed	20 rpm		This speed ensures consistency from batch to batch

4.12 Stability Studies

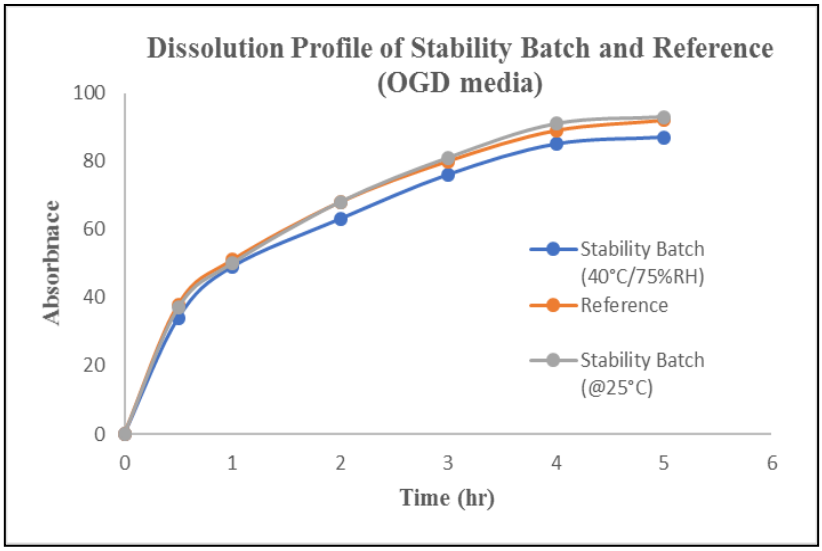
Stability study, as a function of time against a variety of temperatures, humidity, light and combinations of these parameters, is critical for the establishment of recommendations for storage conditions, expiry dates and shelf lives of pharmaceutical products. The primary purpose of the stability testing is to study the overall quality of drug product in terms of strength, purity, identity, safety, apparent degradation, physical changes and their effect on the performance of the product.

Optimized batch of the MR tablet for Model Drug X were placed at 40°C/75%RH and room temperature in HDPE bottles for a period of one month. The evaluation of the optimized batch after one month was shown in **Table 4.64 and Fig. 4.23**.

Table 4.64 Physical Evaluation of Study Batches

Sr No.	Parameter	Specifications	Batch @25°C	Batch @40°C/75%RH
1	Tablet Color	White	White	White
2	Weight	200 ± 5mg	201.2 ± 3mg	200.5± 4mg
3	Hardness	4.5 – 6.0 Kp	5.2 ± 1 Kp	4.9 ± 1.2 Kp
4	Thickness	4.27 ± 0.02	4.27 mm	4.27 mm
5	Diameter	7.9 mm	7.9 ± 0.01mm	7.9 ± 0.01mm

Fig. 4.23 Dissolution Profiles of Stability Batches and Reference Product



Conclusion: From the Table 4.58, it can be concluded that the physical characteristics of the tablets remained unchanged after to room temperature and 40°C/75%RH for one month. Also, from Fig. 4.23 suggests that batch at room temperature is similar to Reference product after one month. But, the batch at 40°C/75%RH showed a reduction in release as compared to the Reference and Batch at room temperature.

The aim of the project was to explore Fluidized Hot Melt Granulation as a platform technology for preparing modified release tablets of BCS class I drug**.**

Literature review suggested that Fluidized Hot Melt Granulation produces granules with good-excellent flow properties. Therefore, drugs which possess poor compressibility, poor flow and high capping tendency were selected in order to verify these literature findings.

Model Drug X belongs to BCS class I and has an anti-anginal effect. Thus, the main effect of the drug is desired in the early morning hours as the angina attacks mostly occur in the morning due to circadian rhythm. Hence, in presented research work modified release formulation was prepared which controls the release of this highly soluble drug. The release was modified by preparation of a hydrophobic matrix tablet using fluidized hot melt granulation technique.

Targeting a QbD based product, a product profile was set and the critical quality attributes were defined. A risk analysis was carried out on the formulation and process variables to identify the potential CQAs that have high impact on the product quality, safety and efficacy.

Product development was initiated with Reference product characterization. Dissolution in different medias were performed which suggested a pH independent release profile of Drug X. Thus the OGD media (5.8 pH) was used for dissolution study during product development stage.

Following this, a Preformulation study was carried out for the Drug X characterization and to check incompatibilities between proposed excipients.

Preliminary trials (one factor at a time) for formulation variable were initiated with Binder screening study. Batches with Hydrogenated Castor Oil and Compritol 888 ATO were evaluated. Based on the data obtained, batch with Hydrogenated Castor Oil showed better powder properties and better compressibility and was thus selected as the binder for the further trials. Due to incomplete release observed in the binder screening batch, a trial with PEG 6000 as a pore former was carried out. PEG 6000, a water soluble polymer, increased the pore formation which helped in complete release of drug. Further, a trial to study the effect of types of fillers was studied and Lactose monohydrate was found to be the better than the other fillers used for the formulation of a MR tablet for Drug X.

After finalizing the formulation components, trials for process optimization were conducted. Granulation time was optimized by studying the mean crushing strength of granules sampled

at different time points during granulation. It was observed that 10min was an optimum time for granulation since no increase in the crushing strength of the granules was found observed post 10min. The trials performed at different processing temperatures suggested that the 95°C was the most optimum granulating temperature since it showed the best similarity (F2) value with reference product dissolution profile.

Trails were also conducted to optimize the milling screen size and the results showed that screen size 1.016mm had the most resemblance to the reference product drug release profile. The Hardness challenge during compression conducted at 20 rpm turret speed on Korsch KL suggested that the release profile from the matrix tablet was independent of the hardness of the tablet.

After the optimization of process variables, DoE trials were conducted to optimize the concentration of Hydrophobic meltable binder (Hydrogenated castor oil) and pore former (PEG 6000). The design used was 3^2 full factorial. The responses selected were drug release at 2hours and drug release at 5 hours. The optimized batches were analyzed using Design Expert® Software v.9.

Comparison of the predicted and practically (check point batch) obtained values was done inorder to validate the model. The multimedia dissolution study of the check point batch was found to be similar to reference product and the F1 and F2 values in OGD media were 3.02 and 77.75 respectively.

Lastly, a control strategy was developed based on the risk assessment, preliminary trials and DoE trials which would ensure product quality when working within the range.

Conclusion: With the application of QbD, a systematic and organized formulation development was possible. FHMG can be successfully used for the preparation of modified release tablets of Drug X. This technique not only control the release of the highly soluble drug but also produces granules with good – excellent flow properties in lesser duration of time as compared to wet granulation method.

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Annexure 1: Release Model Calculation

Drug Dose (D): 60mg

TIME (min)	CUMULATIVE Q	LOG Q	Q *Q	ROOT Q	SQ.Q/100	LOG T	Q/D	LOG Q/D	Root T
0	0	0	0	0	0	0	0	0	0
60	53	1.724	2809	7.280	28.090	1.778	0.883	-0.054	7.746
120	72	1.857	5184	8.485	51.840	2.079	1.200	0.079	10.954
180	81	1.908	6561	9.000	65.610	2.255	1.350	0.130	13.416
240	89	1.949	7921	9.434	79.210	2.380	1.483	0.171	15.492
300	94	1.973	8836	9.695	88.360	2.477	1.567	0.195	17.321

Parameter	Zero Order	First Order	Hixon Crowell	Corse Mayer Pappas	Higuchi Plot
R2 Value	0.8990	0.7319	0.8045	0.6566	0.9881
Slope	0.2795	0.0050	0.0264	0.3557	0.1779
Intercept	22.9048	0.8122	3.3549	-0.6761	-0.7097