Pharmaceutical development report of Dexamethasone Tablets, 20 mg

**Abstract**

**Aim:** In this research, the pharmaceutical development report of Dexamethasone tablets, 20 mg has been discussed in-detail with all relevant sections in sufficiency thus making it eligible to be filed with a regulatory agency. **Scheme:** The overall work flow and the report compilation was done similar to an Abbreviated New Drug Application (ANDA). The Quality Target Product Profile (QTPP) is HEMADY™ (Dexamethasone) Tablets, 20 mg manufactured for Dexcel Pharma Technologies Ltd, Israel and distributed by Acrotech Biopharma Inc, USA. The complete development work was done by Quality by Design (QbD) approach. The composition of drug product was kept similar to the brand product with Lactose Monohydrate as diluent; Corn Starch as binder and disintegrant; Povidone as binder; Sodium Starch Glycollate Type A as disintegrant and Magnesium Stearate as Lubricant. A simple direct blending and compression process was followed to manufacture the drug product. **Optimization:** The particle size distribution (PSD) of Active Pharmaceutical Ingredient (API) was identified as Critical Material Attribute (CMA) – micronized API less than 10 microns needed to achieve Bio-equivalence with the brand product. The blending time was identified as Critical Process Parameter (CPP) – blending time of 15 minutes in Pre-lubrication stage and 5 minutes in Lubrication stage was finalized. The blend flow, hardness and dissolution were identified as Critical Quality Attribute (CQA). **Results & Conclusion:** The manufactured product was found to be stable in bottle and blister pack at International Council for Harmonization (ICH) recommended accelerated stability storage condition at 40°C ± 2°C / 75%RH ± 5% RH for 6 months. The product was found bio-equivalent with the brand product under Fast & Fed condition. To further enable seamless and quality manufacturing of the drug product, systems and controls are put in-place for Microbiological attributes; Control strategy; Product lifecycle management and continuous improvement.

*Keywords: geometric blending, compression, pharmaceutical development report*

**1. INTRODUCTION**

Dexamethasone (Dex), one of the most frequently prescribed glucocorticoids, is widely used for the treatment of a variety of inflammatory skin disorders, rheumatic conditions, respiratory diseases, meningitis, alcohol withdrawal syndrome, high altitude disorder, etc [5,6,7,8]. Dexamethasone Tablets, 20 mg is used as an adjunct therapy for the treatment of Multiple myeloma (Link: https://www.hemady.com/). In US market, Dexamethasone tablets, 20 mg is available as HEMADY™ manufactured for Dexcel Pharma Technologies Ltd, Israel and distributed by Acrotech Biopharma Inc, USA. The unit price is 29 $ per tablet (Link: https://www.drugs.com/price-guide/hemady). In EU market, Dexamethasone tablets, 20 mg is available as Dexamethasone 20 mg soluble tablets manufactured by Aspire Pharma Ltd, UK. The unit price is 3.2 £ (Link: https://www.nice.org.uk/search?q=Dexamethasone). In India, 20 mg strength of Dexamethasone Tablets is not available. The objective of this research work is in bringing a cost-effective alternative to the brand products available in the market. Furthermore the complete development, optimization, design space identification and other specific evaluation will be done by quality by design (QbD) approach as per ICH Q8 (R2) guidance document (Link: https://database.ich.org/sites/default/files/Q8\_R2\_Guideline.pdf). A detailed literature review was done online (Soroush H, 2018; Iswandana R, 2023; Venkatalakshmi Ranganathan, 2018; Ahlam Zaid Alkilani, 2024) on the availability of any formulation or manufacturing work reported on Dexamethasone tablets, 20 mg but none was available except a patent US10,537,585 B2 dated 21st January 2020 of Dexcel Pharma Technologies Ltd. In the patent, an aqueous wet granulation manufacturing process was described to make the tablet using excipients Lactose Monohydrate Impalpable grade, Sodium Starch Glycollate Type A, Corn Starch, Polyvinylpyrrolidone, and Vegetable grade Magnesium Stearate (Link: https://patents.google.com/patent/US10537585B2/en). Based on the available literatures on Dexamethasone Tablets 20 mg as well as on the utility and value the product brings-in for the Multiple Myeloma affected patients, In the current research, a simple direct blending and compression process shall be designed with complete optimization of composition and manufacturing process leading to the final product which will be stable and bio-equivalent to the marketed product. The complete development cycle of the Dexamethasone tablets 20 mg shall be compiled as a Pharmaceutical development report for regulatory submission. Furthermore in every aspect of product development, care shall be taken to achieve a cost-effective and affordable product that will benefit the healthcare services at a large level.

**2. MATERIALS & METHODS**

United States Drug Master File (US DMF) and Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) grade Dexamethasone API was used. All the excipients and packing materials used are of United States Pharmacopoeia (USP) / National Formulary (NF) and Pharmacopoeia Europaea (Ph.Eur) complying grades. Reagents, Solvents, Salts and Chemicals used for analysis are of Analytical reagent grade. Dexamethasone Tablets is official in USP, BP & Ph.Eur. The product monograph was suitably adopted for Physico-chemical and Pharmaceutical analyses. Dissolution methods of testing are officially available in dissolution methods database as well as in USP hence the same was adopted for determination. Other characterization methods viz. Loss on Drying (% LOD), Water by Kf, Disintegration Time (DT), Angle of Repose, Bulk Density (BD), Tapped Density (TD), Carr’s Index (CI), Hausner Ratio (HR), Particle Size Distribution (PSD) by Sieve Analysis, Particle Size Distribution (PSD) by Laser diffraction are done as per compendial general chapter.

**3. METHODOLOGY, RESULTS & DISCUSSION**

In this section the complete development and evaluation is detailed along with results. Elaborate but brief discussion on the experiments and its outcome is provided herein for the benefit of readers.

**3.1 Active Pharmaceutical Ingredient (API)**

Equilibrium solubility study, solution stability, dose – volume study, solid state characterization study, and particle morphology studies were done to understand the API. The details are provided in the table below,

**Table.1 Dexamethasone API Physico-chemical Evaluation**

| **Media** | **Time** | **Mean Solubility** | **Mean Assay** | **Dose / Volume** |
| --- | --- | --- | --- | --- |
| Purified Water | 24 hrs | 0.0784 | 7.78 | 76.53 |
| 25 hrs | 0.0780 | 7.74 |
| 26 hrs | 0.0779 | 7.72 |
| 48 hrs | 0.0780 | 7.74 |
| * 1. N HCl   2. (pH=1.2) | 24 hrs | 0.0790 | 7.88 | 75.95 |
| 25 hrs | 0.0778 | 7.77 |
| 26 hrs | 0.0773 | 7.71 |
| 48 hrs | 0.0787 | 7.85 |
| Acetate buffer  (pH=4.5) | 24 hrs | 0.0790 | 7.86 | 75.95 |
| 25 hrs | 0.0777 | 7.73 |
| 26 hrs | 0.0765 | 7.61 |
| 48 hrs | 0.0785 | 7.81 |
| Phosphate buffer  (pH=6.8) | 24 hrs | 0.0736 | 7.27 | 81.52 |
| 25 hrs | 0.0724 | 7.16 |
| 26 hrs | 0.0718 | 7.09 |
| 48 hrs | 0.0725 | 7.16 |

Based on the above tabulated results, it’s evident on the high solubility, good solution stability upto 48 hrs as well as the drug is less prone to degradation across the physiological pH. Further the drug was evaluated for Crystallinity and polymorphism using Powder X-ray diffraction (PXRD) method as well as crystal morphology testing using Scanning Electron Microscopy and the details are tabulated below,

**Table.2 Dexamethasone API Solid-state & Morphology Evaluation**

|  |  |
| --- | --- |
|  |  |
| Dexamethasone API exhibits Crystallinity.  The characteristic 2θ values in above  PXRD pattern include 7.6°, 13.7°, 14.3°,  15.2°, 15.7°, 17°, 18.6° | The Scanning Electron Microscopy  (SEM) confirms the PXRD findings.  In the above image, characteristic  Crystalline morphology observed. |

Dexamethasone is a BCS Class I / III drug (Link: https://ec.europa.eu/health/documents/community-register/2011/20111024108770/anx\_108770\_en.pdf) hence micronized API was sourced. The API was characterized for Bulk density (BD), Tapped density (TD), Carr’s Index (CI), Hausner ratio (HR), Angle of repose (θ) and Particle size distribution (PSD) by Laser diffraction using Malvern Mastersizer.

**Table.3 Dexamethasone API’s Density, Flow & PSD Characterization**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Bulk**  **Density (g/mL)** | **Tapped**  **Density (g/mL)** | **Carr’s**  **Index**  **(%)** | **Hausner**  **Ratio** | **Angle**  **of**  **Repose**  **(θ)** | **Particle**  **Size**  **Distribution**  **by Malvern** |
| **d90 (µ)** |
| 0.23 | 0.37 | 38 | 1.61 | 31 | 5.87 |

API exhibits good compressibility and densification characteristics. Flow needs to be improved by formulation using excipients. On particle size distribution, the supplied API is micronized with 90% particles in 6 microns. Direct blending and compression process can be explored. Before proceeding for formulation, a risk assessment was performed to evaluate the impact of API attribute on the drug product CQAs. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. The details are shown in the tables below,

**Table.4 Overview of Relative Risk Ranking System**

|  |  |
| --- | --- |
| Low | Broadly acceptable risk. No further investigation is needed. |
| Medium | Risk is acceptable. Further investigation may be needed in order to reduce the risk. |
| High | Risk is unacceptable. Further investigation is needed to reduce the risk. |

**Table.5 Initial Risk Assessment of the Drug Substance Attributes**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug Product CQA’s | Drug Substance Attributes | | | | | | | | |
| Solid State Form | PSD | Hygroscopicity | Solubility | Moisture Content | Residual Solvents | Process Impurity | Chemical Stability | Flow Property |
| Assay | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Content Uniformity | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Dissolution | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Degradation  Products | Low | Low | Low | Low | Low | Low | Low | Low | Low |

The justification for the assigned level of risk is provided in the table below,

Table.6 Justification for the initial risk assessment of the drug substance attributes

| **Drug Substance**  **Attributes** | **Drug Products**  **CQAs** | **Justification** |
| --- | --- | --- |
| Solid State Form | Assay | Drug substance solid state form doesn’t affect the Assay, Content Uniformity, Dissolution and Degradation Products. Hence risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Particle Size  Distribution | Assay | The Particle size of the drug substance used for the development is with D90=NMT 10 microns with satisfactory flow property for a direct blending and compression process. Particle size distribution does not affect Assay, Content Uniformity, Dissolution and Degradation Products. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Hygroscopicity | Assay | Dexamethasone is not hygroscopic. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Solubility | Assay | Solubility doesn’t have impact on assay, degradation products and CU of the drug substance. Since the API is micronized to D90 NMT 10 microns. There will not be any impact on dissolution. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Loss on drying | Assay | Moisture is controlled in the drug substance specification (NMT 0.5% w/w). Thus, it is unlikely to impact assay, content uniformity, dissolution and degradation product. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Residual Solvents | Assay | Residual solvents are controlled in the drug substance specification and comply with USP <467>. At ppm level, residual solvents are unlikely to impact assay, content uniformity, dissolution and degradation product. There are no known incompatibilities between the residual solvents and commonly used excipients. As a result, the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Process Impurities | Assay | Total impurities are controlled in the drug substance specification (NMT 0.5%). Impurity limits comply with ICH Q3A recommendations. Within this range, process impurities are unlikely to impact assay, content uniformity and dissolution. During the excipient compatibility study, no incompatibility between process impurities and commonly used excipients was observed. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Chemical Stability | Assay | The total impurity finalized for the API in the DMF and raw material specification is NMT 0.5%. The drug substance chemical stability is unrelated to Assay, Content Uniformity and Dissolution. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Flow Properties | Assay | Flow property of API is unrelated to Dissolution and Degradation products. API exhibits satisfactory flow and the drug product can be made by a simple direct blending and compression process and hence cannot impact the Assay and Content Uniformity. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |

*PPM: Parts Per Million*

**3.2 Brand Product Characterization**

The brand product was characterized with respect to description, excipients, maximum daily dose (MDD), count details pack configuration; NDC code; tablet image; diameter, weight, thickness, hardness disintegration time and dissolution details of tablets; Based on the brand product characterization, elements for Quality Target Product Profile (QTPP) was arrived viz. Dosage form, Dosage design, Route of administration, Dosage strength, Pharmacokinetics, Stability, Drug product quality attributes, Container closure system, Administration / concurrence with labeling, Alternative methods of administration. Based on the below tabulated results it can be understood that the brand tablets are round, uncoated, having 20% drug concentration. The disintegration time is rapid. Based on the %LOD number, the tablet has a tendency to absorb moisture due to uncoated nature and also due to excipients viz. Povidone and Starch. On the excipients and their role in the brand product includes Lactose Monohydrate as diluent, Corn Starch and Povidone as binder, Sodium Starch Glycollate as disintegrant and Magnesium Stearate as lubricant. The dissolution results show rapid and complete drug release within 10 minutes. The dissolution testing is based on Food and drug administration’s 2018 guidance document. (FDA’s) dissolution guidance, 2018

**Table.7 Brand Product Characterization (RS & RLD)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Description** | **Count per pack** | **Pack** | **Storage** | **NDC** | **Excipients** | **Maximum Daily Dose**  **(MDD)** |
| 20 mg tablet: white, round, biconvex tablets embossed "20" on one side | 24 tablets per bottle  100 tablets per bottle | High density polyethylene bottle (HDPE) with Polypropylene (PP) child resistant closure (CRC) with induction seal liner` | Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant, child resistant container. | 72893-015-24 (24 count)  72893-015-06  (100 count) | Corn Starch, Lactose Monohydrate,  Magnesium Stearate, Povidone K30, Sodium Starch Glycollate Type A | 40 mg per day  (2 tablets per day of 20 mg) |
| **Tablet**  **Image** | **Tablet Diameter**  **(mm)** | **Tablet**  **Weight**  **(mg)** | **Tablet**  **Thickness**  **(mm)** | **Tablet**  **Hardness**  **(kP)** | **Tablet Disintegration Time**  **(min)** | **Tablet Loss On Drying (105°C / Automode)** |
| Hemady 20mg Tablets | Drug Details| Pharmacy | Walgreens | 6.4 | 100-101 | 2.80-2.90 | 4-6 | 2-3 | 3.94 |
| **Dissolution**  USP-II  (Paddle)  50 RPM  500 mL  0.1N HCl  Limit:80%(Q) in 30 minutes | **Time**  **(min)** | 10 | 15 | 20 | 30 | 45 |
| **Mean % drug dissolved, Range, %RSD** | 97  94-99  1.66 | 99  98-100  1.03 | 99  98-100  0.78 | 99  98-100  1.03 | 99  98-101  1.03 |

*°C: degree Celsius; °F: degree Fahrenheit; NDC: National Drug Code; kP: Kilo Pond; HCl: Hydrochloric Acid; Q: Quantity dissolved; RSD: Relative Standard Deviation; USP: United States Pharmacopoeia; RS: Reference Standard; RLD: Reference Listed Drug Product; min: minutes; LOD: Loss on Drying; N: Normality*

(Link:https://www.fda.gov/files/drugs/published/Dissolution-Testing-and-Acceptance-Criteria-for-Immediate-Release-Solid-Oral-Dosage-Form-Drug-Products-Containing-High-Solubility-Drug-Substances-Guidance-for-Industry.pdf). Based on brand drug product, the QTPP elements were targeted to achieve comparable physico-chemical characteristics, drug release, stability and bio-equivalence. The details on QTPP are tabulated below,

**Table.8 Quality Target Product Profile (QTPP)**

| **QTPP Elements** | | **Target** | **Justification** |
| --- | --- | --- | --- |
| Dosage Form | | Tablet | Pharmaceutical equivalence requirement: same dosage form |
| Dosage Design | | Immediate release tablet | Immediate release design needed to meet label claims |
| Route of Administration | | Oral | Pharmaceutical equivalence requirement: same route of administration |
| Dosage Strength | | 20 mg | Pharmaceutical equivalence requirement: same strength |
| Pharmacokinetics | | * 1. Fasting and Fed Study, 90% CI of the PK Parameters Cmax and AUC should fall within Bioequivalence limits | Bioequivalence requirement.  Selected *In-vivo* Studies. |
| Stability | | * 1. At-least 24-month shelf-life at room temperature | Equivalent to or better than RLD shelf life |
| Drug product quality attributes | Physical Attributes | Pharmaceutical equivalence requirement. Must meet the same compendia or other applicable (quality) standards (i.e., identity, assay, purity and quality) | |
| Identification |
| Assay |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Residual Solvents |
| Water Content |
| Microbial Limits |
| Container closure system | | Container closure system qualified as suitable for this drug product | Needed to achieve the target shelf-life and to ensure tablet integrity during shipping |
| Administration / Concurrence with Labeling | | Similar food effect as RLD | RLD labeling indicates no food effect. The product can be taken without regard to food. |
| Alternative methods of administration | | None | None are listed in the RLD label. |

*CI: Confidence Interval; PK: Pharmacokinetics; Cmax: Concentration maximum; AUC: Area Under Curve.*

**3.3 Critical Quality Attributes (CQA)**

The following table summarizes the quality attributes of generic Dexamethasone Tablets and indicates which attributes were classified as drug product critical quality attributes (CQAs). For this product, assay, content uniformity (CU), dissolution and degradation products are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, will be investigated and discussed in detail in subsequent formulation and process development studies. On the other hand, CQAs including identity, residual solvents and microbial limits which are unlikely to be impacted by formulation and/or process variables hence will not be discussed in detail in the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy. In the below table, asterisk (\*) marked Formulation and process variables are unlikely to impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and will be addressed accordingly.

**Table.9 Critical Quality Attribute (CQA) Targets & Justification**

| **Quality Attributes of the Drug Product** | | **Target** | **Is this a CQA?** | **Justification** |
| --- | --- | --- | --- | --- |
| Physical Attributes | Appearance/ Description | Color and shape  acceptable to the patient.  No visual defects observed. | No | Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are considered as not critical. The target is set to ensure patient acceptability. |
| Odor | No unpleasant odor | No | No unpleasant odor coming is observed in the product. No solvents are used in the manufacturing of this product. Therefore, considered as not critical. |
| Size | Similar to RLD | No | For ease of swallowing as well as patient acceptance and compliance, the size of tablet should not be too large, our test product is easily swallowable and tablet size is similar to RLD. |
| Score configuration | Plain | No | The RLD is not a scored tablet; therefore, the generic tablet will not be scored. Score configuration is not critical for our product. |
| Friability | NMT 1.0% w/w | No | Friability is a routine test as per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints. |
| Identification | | Positive for Dexamethasone | Yes\* | Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development. |
| Assay | | 90 – 110 % w/w of label claim | Yes | Assay variability will affect safety and efficacy. Both formulation and Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development. |
| Content Uniformity | | Conforms to USP<905> Uniformity of Dosage Units  Not more than 15.0 | Yes | Content Uniformity variability will affect safety and efficacy. Process variables may affect the Content Uniformity of the drug product. Though Content Uniformity is critical, It will be controlled by effective formulation and process variables. So this CQA will not be discussed during formulation and process development. |
| Dissolution | | Not less than 80 % (Q) of the labeled amount of Dexamethasone (C22H29FO5) is dissolved in 30 minutes. | Yes | Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development. |
| Degradation Products | | 1. Betamethasone NMT 0.5% 2. Desoximetasone NMT 0.5% 3. Dexamethasone Acetate   NMT 0.5%   1. Any Unspecified individual impurity NMT 0.2 % 2. Total impurity   NMT 2.0% | Yes | Organic Impurities can impact safety and must be controlled based on ICH requirements. The target for any unknown impurity is set according to the ICH requirements for this drug product. Formulation and process variables can impact degradation products. Therefore, degradation products will be assessed during product and process development. |
| Residual Solvents | | USP <467> Option 1 | No | Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Therefore, formulation and process variables are unlikely to impact this CQA. |
| Water Content | | NMT 8.0 % w/w | Yes | Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. Therefore, this CQA will be monitored in the finished product and stability analysis of the product. |
| Microbial Limits | | Meets relevant  Pharmacopoeia criteria | Yes\* | Non-compliance with microbial limits will impact patient safety. However, the risk of microbial growth is very low because the formulation process is by direct compression. Therefore; this CQA will not be discussed in detail during formulation and process development. |

*NMT: Not More Than;*

**3.4 Excipient Selection**

Brand listed excipients used. Compatibility screening of brand listed excipients was performed. Closed vials containing the API blended with the excipients were incubated in oven at 40°C/ 75% RH (2nd & 4 weeks) and 55°C (2 weeks). No significant interactions between the drug and the excipients were observed hence Dexamethasone is compatible with brand listed excipients. Details presented below,

**Table.10 Drug – Excipient Compatibility Study**

| **Samples Details** | **Tests** | **Initial** | **Duration / Storage Conditions** | | |
| --- | --- | --- | --- | --- | --- |
| **55 °C**  **2nd Week** | **40°C/75%RH**  **2nd Week** | **40°C/75%RH**  **4th Week** |
| Dexamethasone | Assay % | 99 | 99 | 99 | 100 |
| TI % | 0.11 | 0.13 | 0.14 | 0.14 |
| %WC | 0.24 | 0.31 | 0.32 | 0.30 |
| Dexamethasone + Povidone K30 | Assay % | 96 | 97 | 96 | 98 |
| TI % | 0.12 | 0.11 | 0.14 | 0.12 |
| %WC | 6.28 | 4.86 | 5.14 | 6.44 |
| Dexamethasone + Lactose Monohydrate | Assay % | 99 | 100 | 100 | 100 |
| TI % | 0.09 | 0.13 | 0.21 | 0.14 |
| %WC | 5.16 | 3.99 | 4.01 | 4.02 |
| Dexamethasone+ Sodium Starch Glycollate Type A | Assay % | 98 | 99 | 96 | 99 |
| TI % | 0.12 | 0.19 | 0.15 | 0.13 |
| %WC | 5.33 | 3.83 | 4.90 | 4.13 |
| Dexamethasone+ Corn Starch | Assay % | 98 | 100 | 99 | 98 |
| TI % | 0.11 | 0.16 | 0.13 | 0.13 |
| %WC | 0.12 | 0.48 | 0.45 | 0.37 |
| Dexamethasone+ Vegetable Grade Magnesium Stearate | Assay % | 98 | 99 | 99 | 98 |
| TI % | 0.15 | 0.35 | 0.17 | 0.16 |
| %WC | 2.73 | 2.94 | 2.92 | 2.56 |

*TI: Total Impurity; WC: Water Content*

**3.5 Initial Risk Assessment of Formulation Variables**

Based on the results of excipient compatibility studies product development was initiated. The selection of excipient grade and supplier was based on previous formulation experience and knowledge. The level of excipients used in the formulation was studied in subsequent sections.

**Table.11 Initial Risk Assessment of Formulation Variables**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug Product**  **CQA** | **Formulation Variables** | | | | |
| Povidone K30 | Lactose Monohydrate | Sodium Starch Glycollate Type A | Corn Starch | Vegetable Grade Magnesium Stearate |
| Assay | Low | Low | Low | Low | Low |
| CU | Low | Low | Low | Low | Low |
| Dissolution | Low | Low | Low | Low | Medium |
| Degradation Products | Low | Low | Low | Low | Low |

*CU: Content Uniformity*

**Table.12 Justification for Initial Risk Assessment of Formulation Variables**

| **Formulation**  **Variables** | **Drug Products CQA’s** | **Justification** |
| --- | --- | --- |
| Povidone K30 | Assay | The manufacturing process is by Direct Compression Method; hence dry binder Povidone K30 is used and is compatible with the API as per drug excipient compatibility study. Hence it is highly unlikely that it affects the assay, content uniformity, Dissolution and the degradation profile. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Lactose Monohydrate | Assay | The manufacturing process is by Direct Compression Method and Lactose used is a free-flowing DC grade excipient. it is highly unlikely that it affects the assay, content uniformity. Hence the risk is low. |
| Content Uniformity |
| Dissolution | Lactose Monohydrate can impact dissolution via tablet hardness. However, hardness is controlled during compression with pre-printed optimized limit in Batch manufacturing Record. Hence the risk is low. |
| Degradation Products | Drug-Excipient compatibility was verified against lactose monohydrate, and is compatible with the drug substance. Hence, it will not impact drug product degradation; the risk is low. |
| Sodium Starch Glycollate Type A | Assay | Sodium Starch Glycollate Type A is used as a disintegrant in the composition, which is compatible to API. It is highly unlikely that assay, content uniformity and degradation products gets affected by disintegrant in the composition. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Corn Starch | Assay | The manufacturing process is by Direct Compression Method; hence dry binder and disintegrant Corn Starch is used and is compatible with the API as per drug excipient compatibility study. Hence it is highly unlikely that it affects the assay, content uniformity, Dissolution and the degradation profile. Hence the risk is low. |
| Content Uniformity |
| Dissolution |
| Degradation Products |
| Vegetable Grade  Magnesium Stearate | Assay | Magnesium Stearate is used as a lubricant in the composition and it will not affect assay, content uniformity. Hence the risk is low. |
| Content Uniformity |
| Dissolution | Excessive lubrication may retard dissolution. Hence the risk involved is evaluated as medium. |
| Degradation Products | Drug Excipient compatibility was verified against Magnesium Stearate, and is compatible with the drug substance. Hence it will not impact drug product degradation, the risk is low. |

**3.6 Formulation Development Study# 1**

Based on the API, Brand product and Drug-Excipient evaluation preliminary formulation development trials were done and finalized the following composition and process which showed comparative physico-chemical characteristics and dissolution behavior. The details as follows,

**Table.13 Composition of Dexamethasone Tablets, 20 mg**

|  |  |  |
| --- | --- | --- |
| **S.No** | **Ingredients** | **mg per tablet** |
| 1 | Dexamethasone | 20 |
| 2 | Lactose Monohydrate (Supertab 11 SD) | 55 |
| 3 | Povidone K30 (Kollidon 30) | 3 |
| 4 | Corn Starch (Corn Starch 400L) | 7 |
| 5 | Sodium Starch Glycollate Type A (Explotab) | 14 |
| 6 | Vegetable grade Magnesium Stearate (Hyqual) | 1 |
| **Tablet Weight** | | **100** |

**Manufacturing Process Steps**

Step-1: Sift item no. 2 & 5 through #30 ASTM (American Society for Testing and Materials) mesh and divide into 2 equal parts and load a part into Double Cone Blender.

Step-2: Sift item no. 1,3 & 4 through #30 ASTM mesh and add to blender contents of Step-1 and then load the remaining part of blend from Step-1 and blend at 15 revolution per minute (RPM) for 10 min.

Step-3: Sift the blended material of Step-2 through #30 ASTM mesh and blend at 15 RPM for 15 min. (Prelubrication Stage)

Step-4: Sift item no.6 through #40 ASTM mesh and add to the blender contents of Step-3 and blend at 15 RPM for 5 min. (Lubrication Stage)

Step-5: Compress the blend from Step-4 into tablets using 7 mm circular standard concave punch tooling and finally pack the tablets in bottle and blister pack.

**Table.14 Packing Configuration Details**

| **Count** | **Dunnage** | **Pack Configuration** |
| --- | --- | --- |
| 24’s count bottle | Present | 40cc HDPE container with 33 mm CR closure |
| 100’s count bottle | Present | 75cc HDPE container with 33 mm CR closure |
| 10’s pack blister in a monocarton | Absent | **Base Foil:** EXXTRA 250 MICRON GLASS CLEAR 001  **Lidding Foil:** Crispak PL50 Paper/12PET/25FOIL/07PL HSL |

**3.7 Formulation Development Study# 2**

The goal of this study was to optimize the process and to compare the results with that of prototype batch. The following are the stage-wise characterization done during the process optimization batch.

**Table.15 Stage-wise characterization studies**

|  |  |
| --- | --- |
| **Stage** | **Characterization** |
| Blending | Bulk Density, tapped Density and Particle Size Distribution  Pre-lubrication blending time optimization  Lubricated blending time optimization |
| Compression Process | Tablet Description  Hardness Study  Speed study  Tablet weight, Tablet thickness, Tablet Hardness, Friability, Disintegration time and Content uniformity by stratified sampling as per ASTM E2709/E2810 guidelines. |

The following are the Description, Density and Particle size Distribution (PSD) in final blend of Dexamethasone Tablets, 20 mg.

**Table.16 Final Blend – Characterization details**

|  |  |
| --- | --- |
| Description | White – off white powder |
| Bulk Density (g / mL) | 0.57 |
| Tapped Density (g / mL) | 0.77 |
| Compressibility Index (%) | 26 |
| Hausner’s ratio | 1.35 |
| Particle Size Distribution | % Blend Retained |
| Sieve ASTM # |
| #20 | 0.00 |
| #30 | 1.20 |
| #40 | 0.89 |
| #60 | 0.83 |
| #80 | 8.34 |
| #100 | 8.11 |
| #140 | 47.16 |
| #200 | 24.49 |
| Pan | 8.98 |
| Total | 100.00 |

From the above data it’s evident that the blend has good densification, compressibility and flow property. The granules to fines ratio of the final blend from the presented PSD data is about 20 : 80. The following are the Pre-Lubrication blending time and its blend uniformity results. Based on the below presented results, 15 min blending time was finalized for the Pre-lubrication stage.

**Table.17 Blend Uniformity in Pre-Lubrication Stage**

| **Blender**  **Location** | **Blending Time Points** | | |
| --- | --- | --- | --- |
| **10 min** | **15 min** | **20 min** |
| 1 | 100.68 | 101.60 | 101.00 |
| 2 | 100.96 | 101.00 | 100.40 |
| 3 | 101.30 | 101.86 | 103.74 |
| 4 | 100.78 | 101.48 | 102.40 |
| 5 | 100.72 | 101.64 | 102.28 |
| 6 | 101.24 | 100.72 | 101.60 |
| 7 | 101.86 | 100.46 | 101.28 |
| 8 | 101.78 | 100.84 | 101.24 |
| 9 | 101.30 | 100.58 | 100.80 |
| 10 | 100.92 | 99.88 | 101.38 |
| Mean | 101.14 | 101.00 | 101.60 |
| Min | 100.68 | 99.88 | 100.40 |
| Max | 101.86 | 101.86 | 103.74 |
| %RSD | 0.41 | 0.62 | 0.95 |

The following are the Lubrication blending time and its blend uniformity results. Based on the results 5 min of blending time fixed for the Lubrication stage.

**Table.18 Blend Uniformity in Lubrication Stage**

| **Blender**  **Location** | **Blending Time Points** | | |
| --- | --- | --- | --- |
| **4 min** | **5 min** | **6 min** |
| 1 | 100.56 | 101.18 | 100.30 |
| 2 | 100.92 | 101.90 | 100.02 |
| 3 | 100.24 | 101.46 | 100.00 |
| 4 | 100.50 | 100.64 | 100.86 |
| 5 | 100.80 | 101.84 | 99.64 |
| 6 | 100.40 | 100.34 | 100.50 |
| 7 | 100.30 | 100.58 | 99.84 |
| 8 | 101.28 | 100.22 | 100.48 |
| 9 | 101.20 | 100.02 | 100.00 |
| 10 | 101.08 | 101.06 | 99.82 |
| Mean | 100.72 | 100.92 | 100.14 |
| Min | 100.24 | 100.02 | 99.64 |
| Max | 101.28 | 101.90 | 100.86 |
| %RSD | 0.37 | 0.66 | 0.37 |

The following are ‘Hardness Study’ details, In which the influence of various hardness levels on tablet weight, thickness, percentage friability and disintegration time is provided below,

**Table.19 Hardness Study**

| **Weight (mg)**  **Avg (Range)** | **Thickness (mm)**  **Avg (Range)** | **Hardness (kp)**  **Avg (Range)** | **Friability (%)**  **Avg (Range)** | **Disintegration Time**  **Avg** |
| --- | --- | --- | --- | --- |
| 101.63  (98.01-106.42) | 2.81  (2.79-2.83) | 3.7  (3.1-4.5) | 0.89 | 1 min 22 sec |
| 100.26  (98.55-103.59) | 2.58  (2.54-2.60) | 6.3  (5.6-7.0) | 0.11 | 1 min 20 sec |
| 101.63  (98.01-106.42) | 2.57  (2.54-2.62) | 9.3  (7.2-10.3) | 0.15 | 1 min 30 sec |

From the above tabulated results it’s evident that weight variation observed during compression is less showing good process control. Able to achieve hardness from 3 to 10 kP showing the availability of freedom for compression force during tabletting. The mechanical strength of the manufactured tablet is good and is evident from % Friability. The disintegration time is rapid and the dissolution profile of the tablets made with varying hardness was found comparable to marketed brand product.

**Table.20 Hardness study on dissolution comparing with brand product**

USP-II (Paddle), 50 RPM, 500 mL, 0.1N HCl, Limit: 80%(Q) in 30 min.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Brand** | **Time**  **(min)** | 10 | 15 | 20 | 30 | 45 |
| **Mean % drug dissolved, Range, %RSD** | 97  94-99  1.66 | 99  98-100  1.03 | 99  98-100  0.78 | 99  98-100  1.03 | 99  98-101  1.03 |
| **Low Hardness** | **Mean % drug dissolved, Range, %RSD** | 89 84-93 4.02 | 94 89-95 2.81 | 96 95-97 1.05 | 97 96-99 1.01 | 98  97-99 0.84 |
| **Target Hardness** | **Mean % drug dissolved, Range, %RSD** | 92 90-97  2.77 | 97 96-99 0.86 | 98 98-100 0.74 | 99 99-100 0.66 | 100 99-101 0.60 |
| **High Hardness** | **Mean % drug dissolved, Range, %RSD** | 90 86-92 2.20 | 96 95-96 0.55 | 98 97-99 0.70 | 99 98-100 0.58 | 100 99-101 0.64 |

The following are the ‘Speed Study’ details of Dexamethasone Tablets, 20 mg. In this study the influence of machine speed levels (turret speed of compression machine) on tablet weight variation and uniformity of dosage units (UOD) variation; content uniformity by stratified sample as per ASTM E2709/E2810 guidance and finally content uniformity evaluation in composite sampling is provided below,

**Table.21 Speed Study & Weight Variation**

| **Speed Study (RPM)& Weight Variation (mg)** | | | | |
| --- | --- | --- | --- | --- |
| **Mean, Range, %RSD** | | | | |
| **10 RPM** | **20 RPM** | **30 RPM** | **40 RPM** | **50 RPM** |
| 100  98-102  1.08% | 102  99-105  2.02% | 102  100-104  0.98% | 102  100-104  0.98% | 101  98-104  1.52% |

The compression process exhibited less weight variation during tabletting at varying machine speed. This shows the blend flow during tabletting is good and the weight variation due to density changes / segregation of components in the blend was not observed. Further it was decided to study the influence of speed on Content Uniformity or Uniformity of Dosage Units as per USP <905> and the details are as follows which showed good content uniformity of drug in the drug product (tablets) throughout the compression process which is clearly evident from ‘AV’ (Acceptance Value).

**Table.22 Speed Study & Content Uniformity or Uniformity of Dosage Units (UOD)**

| **Speed Study (RPM) & Uniformity of Dosage Units** | | |
| --- | --- | --- |
| **Mean, Range, %RSD; AV limit = NMT 15.** | | |
| **Low (10 RPM)** | **Optimum (30 RPM)** | **High (50 RPM)** |
| 100.29  98.94-101.74  0.93%  AV (L1) – 2.2 | 101.08  99.74-102.30  0.90%  AV (L1) – 2.2 | 100.05  98.06-101.62  1.17%  AV (L1) – 2.8 |

Also further to ensure the content uniformity as per regulatory requirements, samples were collected for analysis of Content Uniformity by stratified sampling as per ASTM E2709/E2810 guidance and the details are presented in the table below. In this evaluation also the batch comfortably passes the requirements ensuring the content uniformity of the manufactured drug product.

**Table.23 Content Uniformity by Stratified sampling as ASTM E2709/E2810 guidance**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **ASTM E2810 Statistics** | | | **Acceptance Limits** | | | **Variance Components** | | | | | |
| **Min (%)** | **Max**  **(%)** | **Overall**  **Mean**  **(%)** | **Between**  **Location**  **SD** | **Within**  **Location**  **SD** | **Lower**  **(%)** | **Upper**  **(%)** | **Pass**  **(Or)**  **Fail** | **Between**  **Location** | | **Within Location** | | **Total** | |
| **SD** | **% Total** | **SD** | **% Total** | **SD** | **% Total** |
| 97.6 | 104.0 | 101.24 | 1.17 | 1.20 | 89.1 | 110.9 | Yes | 0.95 | 38.4 | 1.20 | 61.6 | 1.53 | 100.0 |

*Min: Minimum; Max: Maximum; SD: Standard Deviation;*

Once the compression process is completed, composite sampling was done to evaluate Content uniformity. This content uniformity testing is representing the drug uniformity of the whole batch. The details are provided below. The composite CU testing comfortably passes the AV limits as per USP.

**Table.24 Content Uniformity for composite sampling**

|  |  |
| --- | --- |
| **Min** | 98.88 |
| **Max** | 102.06 |
| **AV Value** | 1.06 |
| **%RSD** | 2.5 |

**3.8 Formulation Development Study# 3**

This formulation development study #3 was conducted to evaluate the impact of three (3) excipients. The Excipients selected for the study are Lactose Monohydrate (Supertab 11SD) as diluent, Sodium Starch Glycollate Type A (Explotab) as Disintegrant, Magnesium Stearate (Hyqual, Vegetable source) as Lubricant on three (3) responses viz, final blend flow (measured by angle of repose), final blend compressibility (measured by hardness of tablet) and drug release (dissolution of tablet).Formulation development studies were conducted at laboratory scale (Batch size of 2000 units). Table shown below details the equipment and the associated process parameters used in these studies. The goal of the Formulation Development Study was to evaluate the risk assessment of the selected excipients with response of critical parameters in formulation.

**Table.25: Equipment and Fixed Process Parameters**

|  |  |
| --- | --- |
| **Process Step** | **Equipment** |
| Sifting & Blending | * Vibrosifter equipped with mesh #30 * Double Cone Blender at 15 RPM for 10 minutes. * Vibrosifter equipped with mesh #30. * Double Cone Blender at 15 RPM for 15 minutes. * Vibrosifter equipped with #40 mesh. * Double Cone Blender at 15 RPM for 5 minutes. |

The significant factors was considered as optimizing the risk with level of change in quantity of Diluent level, Disintegrant level and Lubricant level to understand if there was any interaction of these variables with response to Dissolution, Hardness and Angle of Repose in the formulations. This study also sought to establish the robustness of the proposed formulation. An OFAT (One Factor At A Time) was used to study the impact of these three (3) formulation factors on the response variables listed in below mentioned table. The effect of diluent, Lactose Monohydrate (Supertab 11SD) concentration in the formulation was evaluated with the range of 45% to 65%. Effect of disintegrant, Sodium Starch Glycollate Type A (Explotab) Concentration in the formulation was evaluated with the range of 12% to 16%. Effect of Lubricant, Magnesium Stearate (Hyqual) Concentration in the formulation was evaluated with the range of 0.5% to 1.5%.This formulation study evaluates critical attributes on final proposed formula and its interaction on selected responses of the formulation.

**Table.26: Design of OFAT to study composition & process variables**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S.No** | **Ingredients** | | **-1** | **0** | **+1** |
| 1 | Dexamethasone | | 20 | 20 | 20 |
| 2 | Lactose Monohydrate (Supertab 11 SD) | | 45 | 55 | 65 |
| 3 | Povidone K30 (Kollidon 30) | | 3 | 3 | 3 |
| 4 | Corn Starch (Corn Starch 400L) | | 7 | 7 | 7 |
| 5 | Sodium Starch Glycollate Type A (Explotab) | | 12 | 14 | 16 |
| 6 | Vegetable grade Magnesium Stearate (Hyqual) | | 0.5 | 1 | 1.5 |
| **Tablet Weight** | | |  | **100** |  |
|  | **Response** | **Goal** | **Acceptable Ranges** | | |
| R1 | Dissolution @ 30 minutes (%) | Minimum | 80% Q | | |
| R2 | Tablet Hardness @ 6 kP | Range | 3-10 kp | | |
| R3 | Angle of Repose (θ) | Maximum | NMT 40 | | |

The formulation variable levels are followed with acceptance change limit of diluent, disintegrant and lubricant concentration level mentioned in SUPAC guidelines. A constant tablet weight of 100 mg was used with the filler amount adjusted to achieve the target weight. Below mentioned table summarizes the factors and responses studied. For each batch, the blend was studied for flow property (Angle of Repose), compressibility (in terms of hardness) and drug release (dissolution). The experiment results are provided in the table below,

**Table.27: Experiments & results of OFAT to study composition & process variables**

| **Level** | **Formulation variables** | | | | | | **Response** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **API** | **LM** | **PVPK30** | **CS** | **SSG** | **MgS** | **Dissolution** | **Hardness** | **Angle of Repose** |
| 0 | 20 | 55 | 3 | 7 | 14 | 1 | 99 | 3-10 | 33 |
| -1 | 20 | **45** | 3 | **17** | 14 | 1 | 96 | **3-7** | **39** |
| +1 | 20 | **65** | 3 | **0** | 14 | 1 | 97 | 3-9 | 34 |
| -1 | 20 | **57** | 3 | 7 | **12** | 1 | 98 | 3-9 | 34 |
| +1 | 20 | **55** | 3 | 7 | **16** | 1 | 99 | 3-9 | 33 |
| -1 | 20 | **54.5** | 3 | 7 | 14 | **0.5** | 98 | 3-10 | 34 |
| +1 | 20 | **55.5** | 3 | 7 | 14 | **1.5** | **93** | **3-7** | 34 |

*API: Active Pharmaceutical Ingredient; LM: Lactose Monohydrate; PVPK30: Polyvinyl Pyrrolidone K30; CS: Corn Starch; SSG: Sodium Starch Glycollate; MgS: Magnesium Stearate.*

Totally 6 experiments was conducted by OFAT method, Diluent (Lactose Monohydrate – Supertab 11 SD) play a very key role in characteristics viz. hardness and flow property. At -1 level of diluent, significant change in hardness, compressibility and blend flow observed. Even with SUPAC Level 2 changes in diluent amount, the composition complied with predetermined acceptable ranges. Disintegrant (Sodium Starch Glycollate Type A – Explotab) play a very key role in characteristics viz. Dissolution. Even with SUPAC Level 2 changes in disintegrant amount, the composition complied with predetermined acceptable ranges. Lubricant (Magnesium Stearate – Hyqual) plays a key role in characteristics viz. Dissolution & Hardness. At +1 level of lubricant, significant change in dissolution and hardness observed. Even with SUPAC Level 2 changes in lubricant amount, the composition complied with predetermined acceptable ranges. Hence based on the experiments and its outcome, the diluent, disintegrant and lubricant levels can be very well varied and the design space for them is ± 10%, 2% & 0.5% respectively. At these levels, the composition and process behaves the same way as the centre point (0 level).

**3.9 Finalized Formulation**

The following is the finalized composition of Dexamethasone Tablets, 20 mg

**Table.28 Composition of Dexamethasone Tablets, 20 mg**

|  |  |  |
| --- | --- | --- |
| **S.No** | **Ingredients** | **mg per tablet** |
| 1 | Dexamethasone | 20 |
| 2 | Lactose Monohydrate (Supertab 11 SD) | 55 |
| 3 | Povidone K30 (Kollidon 30) | 3 |
| 4 | Corn Starch (Corn Starch 400L) | 7 |
| 5 | Sodium Starch Glycollate Type A (Explotab) | 14 |
| 6 | Vegetable grade Magnesium Stearate (Hyqual) | 1 |
| **Tablet Weight** | | **100** |

**4.0 Updated Risk Assessment of Formulation Variables**

Acceptable ranges for the high risk formulation variables have been established and are included in the control strategy.

**Table.29 Updated risk assessment of the formulation variables**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug Product**  **CQA** | **Formulation Variables** | | | | |
| Povidone K30 | Lactose Monohydrate | Sodium Starch Glycollate Type A | Corn Starch | Vegetable Grade Magnesium Stearate |
| Assay | Low | Low | Low | Low | Low |
| CU | Low | Low | Low | Low | Low |
| Dissolution | Low | Low | Low | Low | **\*Low** |
| Degradation Products | Low | Low | Low | Low | Low |

*\* The level of risk was reduced from the initial risk assessment.*

Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated below,

**Table.30 Justification for the Upated risk assessment of the formulation variables**

|  |  |  |
| --- | --- | --- |
| **Formulation**  **Variables** | **Drug Products CQA’s** | **Justification** |
| Magnesium Stearate | Dissolution | Excessive lubrication may retard dissolution. Lubricant concentration in the drug product is 0.5%. The effect of Lubricant concentration in the formulation was evaluated in Formulation development #3. And it is concluded that the change in lubricant concentration does not impact the Dissolution. The Lubrication time is evaluated in process optimization batches and discussed in detail. The lubrication time is controlled by Pre printed optimized blending time in Batch manufacturing Record and the hence the risk is low. |

**4.1 Overages**

There are no overages used in the formulation of Dexamethasone Tablets, 20 mg.

**4.2 Exhibit Batch**

Based on the formulation development studies discussed before, it was decided to perform submission batches / exhibit batches for stability, BE study and regulatory submission purpose. The details are as follows. Totally 3 batches were made with 2 different lots of API to qualify for exhibit batch regulatory requirements. The following are the Description, Density and Particle size Distribution (PSD) in final blend of Dexamethasone Tablets, 20 mg.

**Table.31 Final Blend – Characterization details**

|  |  |  |  |
| --- | --- | --- | --- |
| Description | White – off white  powder | White – off white  powder | White – off white  powder |
| Bulk Density (g / mL) | 0.56 | 0.55 | 0.57 |
| Tapped Density (g / mL) | 0.79 | 0.77 | 0.76 |
| Compressibility Index (%) | 26 | 26 | 25 |
| Hausner’s ratio | 1.35 | 1.4 | 1.33 |
| Particle Size Distribution | % Blend Retained | % Blend Retained | % Blend Retained |
| Sieve ASTM # |
| #20 | 0.00 | 0.00 | 0.00 |
| #30 | 1.38 | 1.71 | 1.52 |
| #40 | 0.97 | 0.93 | 0.91 |
| #60 | 0.91 | 0.88 | 0.94 |
| #80 | 9.52 | 8.89 | 8.97 |
| #100 | 11.8 | 7.97 | 8.63 |
| #140 | 48.64 | 46.92 | 48.01 |
| #200 | 23.65 | 23.29 | 25.05 |
| Pan | 3.13 | 9.41 | 5.97 |
| Total | 100.00 | 100.00 | 100.00 |

**Table.32 Blend Uniformity in Lubrication Stage**

| **Location** | **5 min** | **5 min** | **5 min** |
| --- | --- | --- | --- |
| 1 | 100.68 | 101.50 | 101.00 |
| 2 | 101.02 | 101.54 | 100.97 |
| 3 | 101.68 | 100.28 | 101.37 |
| 4 | 101.28 | 100.85 | 101.99 |
| 5 | 101.03 | 100.59 | 100.83 |
| 6 | 101.25 | 101.49 | 101.04 |
| 7 | 101.36 | 101.13 | 101.66 |
| 8 | 102.16 | 100.80 | 101.68 |
| 9 | 101.26 | 100.69 | 101.99 |
| 10 | 100.98 | 101.81 | 101.75 |
| Mean | **101.27** | **101.07** | **101.43** |
| Min | **100.68** | **100.28** | **100.83** |
| Max | **102.16** | **101.81** | **101.99** |
| %RSD | **0.40** | **0.49** | **0.43** |

From the above data it is evident that all three exhibit batches showed similar density, flow and particle size distribution characteristics. On the Lubrication blending time and its blend uniformity results, 5 min of blending time is working fine for the Lubrication stage. The following are ‘Tabletting Study’ details, In which the observed tablet weight, thickness, percentage friability and disintegration time is provided below for the 3 exhibit batches,

**Table.33 Tabletting Study & Physical Characteristics Evaluation**

| **Weight (mg)**  **Avg (Range)** | **Thickness (mm)**  **Avg (Range)** | **Hardness (kp)**  **Avg (Range)** | **Friability (%)**  **Avg (Range)** | **Disintegration Time**  **Avg** |
| --- | --- | --- | --- | --- |
| 101.05  (98.12-104.21) | 2.41  (2.38-2.55) | 5.7  (4.1-7.5) | 0.3 | 1 min 2 sec |
| 100.17  (98.09-102.59) | 2.48  (2.40-2.63) | 6.6  (5.6-9.0) | 0.3 | 58 sec |
| 100.03  (97.01-101.42) | 2.44  (2.42-2.59) | 6.1  (4.2-82) | 0.4 | 1 min 3 sec |

From the above tabulated results it’s evident that weight variations, hardness achievability, mechanical strength of the manufactured tablets are good. The disintegration time and dissolution is rapid and complete for all the batches and is found comparable to marketed brand product.

**Table.34 Tabletting Study & Dissolution Evaluation**

USP-II (Paddle), 50 RPM, 500 mL, 0.1N HCl, Limit: 80%(Q) in 30 min.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Brand** | **Time**  **(min)** | 10 | 15 | 20 | 30 | 45 |
| **Mean % drug dissolved, Range, %RSD** | 97  94-99  1.66 | 99  98-100  1.03 | 99  98-100  0.78 | 99  98-100  1.03 | 99  98-101  1.03 |
| **EB-1** | **Mean % drug dissolved, Range, %RSD** | 74  (70-75)  2.19 | 92  (89-93)  1.5 | 96  (94-98)  1.37 | 97  (95-99)  1.25 | 96  (95-98)  1.13 |
| **EB-2** | **Mean % drug dissolved, Range, %RSD** | 73  (67-77)  3.72 | 92  (88-95)  2.03 | 97  (94-99)  1.55 | 98  (96-100)  1.36 | 98  (96-100)  1.11 |
| **EB-3** | **Mean % drug dissolved, Range, %RSD** | 74  (65-77)  4.52 | 93  (92-95)  1.25 | 98  (96-99)  1.08 | 99  (97-100)  1.17 | 98  (97-100)  1.09 |

The following are the details of Dexamethasone Tablets, 20 mg for content uniformity by stratified sample as per ASTM E2709/E2810 guidance. In this evaluation all the 3 batches comfortably passes the requirements ensuring the content uniformity of the manufactured drug product.

**Table.35 Content Uniformity by Stratified sampling as ASTM E2709/E2810 guidance**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **ASTM E2810 Statistics** | | | **Acceptance Limits** | | | **Variance Components** | | | | | |
| **Min (%)** | **Max**  **(%)** | **Overall**  **Mean**  **(%)** | **Between**  **Location**  **SD** | **Within**  **Location**  **SD** | **Lower**  **(%)** | **Upper**  **(%)** | **Pass**  **(Or)**  **Fail** | **Between**  **Location** | | **Within Location** | | **Total** | |
| **SD** | **% Total** | **SD** | **% Total** | **SD** | **% Total** |
| 92.5 | 103.5 | 100.43 | 0.71 | 1.60 | 88.9 | 111.1 | Pass | 0.00 | 0.0 | 1.60 | 100.0 | 1.60 | 100.0 |
| 90.8 | 103.0 | 100.50 | 0.97 | 1.47 | 89.0 | 111.0 | Pass | 0.47 | 9.3 | 1.47 | 90.7 | 1.54 | 100.0 |
| 96.7 | 102.3 | 100.23 | 0.60 | 0.91 | 87.2 | 112.8 | Pass | 0.30 | 9.8 | 0.91 | 90.2 | 0.95 | 100.0 |

Once the compression or tabletting process is completed, the product was subjected to finished product or Initial analysis for Assay, RS, Water by Kf and Microbial load and the details as follows, Also the tablets from 3 batches manufactured complied to the description of white to off white circular biconvex tablets with 20 on one side and plain on the other side. All the manufactured batches passed for Assay (drug content), degradation profile (HUI & TI), Water content (Moisture) & Microbial content.

**Table.36 Finished Product Analysis or Initial Analysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Assay, %** | **HUI, %** | **TI, %** | **Water by Kf, %** | **TAMC, cfu/g** | **TYMC, cfu/g** | **Escherichia coli** |
| 100.5 | 0.080 | 0.169 | 4.16 | LT 10 | LT 10 | Absent |
| 100.8 | 0.068 | 0.155 | 4.37 | LT 10 | LT 10 | Absent |
| 100.4 | 0.076 | 0.162 | 4.27 | LT 10 | LT 10 | Absent |

*HUI: Highest Unknown Impurity; TI: Total Impurity; TAMC: Total Aerobic Microbial Count; TYMC: Total Yeast And Mould Count; LT: Less Than; CFU: Colony Forming Units;*

The manufactured tablets of all the batches were packed in bottle and blister pack and subjected to stability testing at Accelerated storage condition at 40°C / 75% RH for 6 months. The stability data results showed the product was stable physico-chemically hence the product qualifies for the shelf life at room temperature for 24 months. The details as below.

**Table.37 Accelerated Stability Storage Analysis**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Period** | **Pack** | **AY, %**  **90-110** | **Disso**  **‘Q’ Point**  **NLT 85** | **HUI,**  **%**  **NMT 0.2** | **TI,**  **%**  **NMT 2** | **WKf, %**  **NMT 7** | **TAMC, cfu/g** | **TYMC, cfu/g** | **E. coli** |
| Initial | NA | 100.5 | 99 | 0.080 | 0.169 | 4.16 | LT 10 | LT 10 | Absent |
| 100.8 | 97 | 0.068 | 0.155 | 4.37 | LT 10 | LT 10 | Absent |
| 100.4 | 98 | 0.076 | 0.162 | 4.27 | LT 10 | LT 10 | Absent |
| ACC 1st Month | Bottle | 100.4 | 100 | 0.098 | 0.175 | 4.73 | LT 10 | LT 10 | Absent |
| 101.3 | 99 | 0.073 | 0.161 | 4.42 | LT 10 | LT 10 | Absent |
| 101.2 | 98 | 0.081 | 0.169 | 4.16 | LT 10 | LT 10 | Absent |
| ACC 1st Month | Blister | 99.37 | 99 | 0.089 | 0.171 | 4.68 | LT 10 | LT 10 | Absent |
| 98.8 | 99 | 0.074 | 0.153 | 4.81 | LT 10 | LT 10 | Absent |
| 100.4 | 98 | 0.072 | 0.160 | 4.77 | LT 10 | LT 10 | Absent |
| ACC 6th Month | Bottle | 100.3 | 98 | 0.110 | 0.257 | 5.13 | LT 10 | LT 10 | Absent |
| 99.6 | 97 | 0.117 | 0.282 | 5.62 | LT 10 | LT 10 | Absent |
| 100.2 | 97 | 0.139 | 0.279 | 5.18 | LT 10 | LT 10 | Absent |
| ACC 6th Month | Blister | 100.4 | 97 | 0.101 | 0.269 | 5.45 | LT 10 | LT 10 | Absent |
| 101.3 | 98 | 0.112 | 0.285 | 5.78 | LT 10 | LT 10 | Absent |
| 101.2 | 97 | 0.121 | 0.298 | 5.91 | LT 10 | LT 10 | Absent |

The exhibit batch size is 200,000 tablets with blender capacity of 50 L used and for the commercial it has been decided to manufacture 2000,000 tablets for which 600 L blender shall be used. The exhibit and commercial batches will be made in the same compression machine and packing machines (bottle & blister). Hence there will not be any surprises in the process control or on the quality output and the facility has the necessary resources to scale up the drug product from exhibit batch to commercial scale.

The manufactured product was subjected to bio-equivalence study under fast and fed condition against the marketed brand product in healthy human volunteers. Conducted an open label, single-dose, randomized, two-treatment, twoperiod crossover study to compare the marketed brand product and test product under fasting and fed conditions in 36 healthy human volunteers with equal of males and non-pregnant females. Under fasting conditions, no food was allowed from at least 10 hours before dosing until at least 4 hours after dosing. Under fed conditions, a high-fat, high-calorie meal was served 30 minutes prior to dosing and subjects fasted for at least 4 hours after dosing. The sampling time points include predose (0 hr), and at 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10.0, 12, 16, 20, 24, and 36 hours post-dose. Summary BE resuts of the PK parameters of dexamethasone are presented in Table below. The manufactured drug product, Dexamethasone Tablets, 20 mg was found to be bio-equivalent to the marketed brand product.

**Table.38 Bio-equivalence Evaluation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **PK**  **Parameters** | **Intra subject CV** | **T/R Ratio** | **90% Confidence Interval For Test Vs Reference** | **Posteriori Power** |
| FAST | CMAX | 15.52% | 89.48% | 83.98% to 95.34% | 99.95% |
| AUCT | 9.28% | 101.19% | 97.41% to 105.11% | 100.0% |
| AUCI | 8.53% | 100.43% | 96.98% to 104.01% | 100.0% |
| FED | CMAX | 10.67% | 95.88% | 91.9% to 100.03% | 100.0% |
| AUCT | 9.11% | 101.01% | 97.42% to 104.74% | 100.0% |
| AUCI | 8.37% | 101.20% | 97.88% to 104.62% | 100.0% |

*CMAX: Concentration Maximum; AUCT: Area Under the Curve at Time T; AUCI: Area Under the Curve from time T to infinity; T/R: Test / Reference; CV: Coefficient of variation;*

**4.3 Microbiological Attributes**

An accelerated stability study of the exhibit batch demonstrated that the drug product has low water activity and is not capable of supporting microbial growth. Routine microbiological testing is unnecessary due to the low water activity of the product and controls on incoming raw materials.

**4.4 Control Strategy**

The control strategy for the commercial manufacturing of Dexamethasone Tablets, 20 mg is proposed and presented herewith. The control strategy includes Dexamethasone and excipient material attributes to be controlled, in-process controls, the risk process parameter ranges studied during development and the proposed operating ranges for commercial manufacture. The purpose of the controls is also briefly discussed. The incoming raw material was controlled as per the quality control specifications and drug product manufacturing is controlled by manufacturing records. The specifications for Dexamethasone Tablets, 20 mg is presented below,

**Table.39 Specification for Dexamethasone Tablets, 20 mg**

| **S. No & Stage** | **Test** | **Specification** |
| --- | --- | --- |
| Lubricated Blend | Description | White to off white powder |
| Bulk Density | Not less than 0.4g/mL and Not more than 0.8g/mL |
| Tapped Density | Not less than 0.6g/mL and Not more than 0.9g/mL |
| Particle Size Distribution  (Sieve Analysis) | % retains on #60 mesh: Not More than 10 %  % retains on #100 mesh: Not More than 40%  % retains on #200 mesh: Not More than 50% |
| Water content by KF | Not more than 8.0% |
| Blend Uniformity | The Relative Standard Deviation should not more than 5.0 %, all individuals and mean should be Not less than 90% and Not more than 110.0% of the labeled amount of Dexamethasone (C22H29FO5). |
|  | | |
| **S.No & Stage** | **Test** | **Specification** |
| Compressed Tablets | Description | White to off white, round shaped, biconvex tablets debossed with “20” on one side and plain on the other side. |
| Compression Parameters | Target tablet unit weight: 100.00 mg  Individual tablet weight range: 92.50 mg – 107.50 mg  Target hardness: 6.0 kp  Individual tablet hardness range: 3.0 – 10.0 kp  Target thickness: 2.60 mm  Individual tablet thickness range: 2.00 mm – 3.00 mm |
| Friability | Not more than 1.0% (in 4 minutes) |
| Disintegration Time (minutes) | Not more than 15 minutes |
| Identification Test A:  (By Thin Layer Chromatography) | The Rf value of the principal spot of the sample solution corresponds to that of standard solution. |
| Identification Test B:  (By HPLC) | The retention time of the major peak of the sample solution corresponds to that of standard solution, as obtained in the assay. |
| Uniformity of Dosage Units, Content Uniformity  (By HPLC) | Acceptance Value : Not more than 15.0 |
| Content Uniformity By Stratified Sampling | Perform and inter results as per ASTM E2709/E2810 guidance |
| Dissolution (By HPLC) | Not less than 80% (Q) of the labeled amount of Dexamethasone (C22H29FO5) is dissolved in 30 minutes. |
| Assay | Not less than 90.0% and Not more than 110.0% of labeled amount of Dexamethasone (C22H29FO5) |
| Water content (By KF) (%w/w) USP <921 Method Ia> | Not more than 8.0% |
| Organic Impurity | Any other impurity – Not more than 0.5%  Highest Unknown Impurity – Not more than 0.2%  Total Impurity – Not more than 2.0% |
| Microbial Content | Total aerobic microbial count – Not more than 1000 cfu/g  Total combined mold and yeast count – Not more than 100 cfu/g  Escherichia coli – Absent |
| Residual Solvents | Should meet the USP <467> requirement (option-1) |
| Elemental Impurities | Should meet the USP <232> requirement (option-2b) |
| Compressed  Tablets (Intact)  Stability | Description | White to off white, round shaped, biconvex tablets debossed with “20” on one side and plain on the other side. |
| Identification Test A:  (By Thin Layer Chromatography) | The Rf value of the principal spot of the sample solution corresponds to that of the standard solution. |
| Identification Test B:  (By HPLC) | The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay |
| Water content by KF | Not more than 9.0% |
| Dissolution  (By HPLC) | Not less than 80% (Q) of the labeled amount of Dexamethasone (C22H29FO5) is dissolved in 30 minutes |
| Disintegration Time (minutes) | Not More than 15 minutes. |
| Assay | Not less than 90.0% and Not more than 110.0% of labeled amount of Dexamethasone (C22H29FO5) |
| Organic Impurity | Any other impurity – Not more than 0.5%  Highest Unknown Impurity – Not more than 0.2%  Total Impurity – Not more than 2.0% |
| Microbial Content | Total aerobic microbial count – Not more than 1000 cfu/g  Total combined mold and yeast count – Not more than 100 cfu/g  Escherichia coli – Absent |

**4.5 Product Lifecycle Management and Continual Improvement**

Upon approval, the manufacturing process for Dexamethasone Tablets, 20 mg will be validated using the lifecycle approach that employs risk-based decision making throughout the drug product lifecycle as defined in the FDA & EMEA process validation guidance. The manufacturing facility is designed according to cGMP regulations on Building and Facilities. Activities will be taken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. The protocol for process performance qualification will be written, reviewed, approved, and then executed to demonstrate that the commercial manufacturing process performs as expected. The goal of this stage (Continued Process Verification) is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. Throughout the product lifecycle, the manufacturing process performance will be monitored to ensure that it is working as anticipated to deliver the product with desired quality attributes. Process stability and process capability will be measured and evaluated. If any unexpected process variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control. The additional knowledge gained during routine manufacturing will be utilized for adjustment of process parameters as part of the continual improvement of the drug product. As a commitment, the regulatory agency will be notified in accordance with CFR & EMEA guidelines regarding each change in each condition beyond the variability already provided in this report

**5. CONCLUSION**

In this research, Dexamethasone Tablets, 20 mg was successfully formulated and manufactured. It all started with the identifying cost-effective sourcing of API. API characterization was done which showed the suitability of direct blending and compression process. Since API being BCS Class I / III, micronized API was used this formed the basis of Critical Material Attribute (CMA). Marketed brand product was sourced and characterized; this formed the basis for Quality Target Product Profile (QTPP). Based on API and brand product characterization, risk assessment and Critical Quality Attributes (CQA) were decided. In the composition, brand listed excipients were used but the suitability of the excipients were tested and confirmed through drug – excipient compatibility study. A composition with Lactose Monohydrate as diluent, Povidone K30 and Corn Starch as binder, Sodium Starch Glycollate Type A as disintegrant and Magnesium Stearate as lubricant by direct blending and compression process was designed. The selected composition and process was further optimized by doing design of experiments (DOE) using One Factor At A Time (OFAT) approach. In the manufacturing process blending time formed the basis for Critical Process Parameter (CPP). In the composition, diluent, disintegrant and lubricant were identified and optimized for CQA’s – dissolution, angle of repose & hardness; accordingly design space for the identified excipients were arrived based on SUPAC IR guidance. Then submission batches was manufactured and found to be stable in the intended packing configuration at 40°C / 75%RH for 6 months. The manufactured tablet was found to be bio-equivalent to the marketed brand product. The unit price of the manufactured tablet was calculated and was found to be 13.13 INR per tablet. A Pharmaceutical development report (PDR) was drafted herein encompassing every aspect of activity done from development upto exhibit batch / submission batch manufacturing. This report is now ready to be filed with any regulatory agency.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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