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Quality by Design (QbD) Approach for Formulation Development of Hydralazine Hydrochloride Tablets

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ABSTRACT

The main aim of the present study was to develop a robust and stable immediate release tablet formulation of Hydralazine hydrochloride using quality by design (QbD) approach. Critical material attributes and critical process parameters were identified and linked to the critical quality attributes (CQA's) of the drug product/formulation. Experimental trials were designed using factorial design technique with considering critical material attributes (CMA's) and critical process attributes (CPP's). Physicochemical characterization and drug excipient compatibility studies were performed. Flow characteristics and compressibility of blend material were tested before tablets were compressed by direct compression method. Weight variation, diameter, thickness, hardness, %friability, disintegration time of compressed tablets were evaluated for physical characterization. Design space was identified and risk factors mitigated after the implementation of control strategy.

Keywords: Quality by design, Critical quality attributes, Critical material attributes, Design space, IR tablets

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INTRODUCTION

In the 21st century, FDA initiated Quality by design (QbD) and Process analytical technology (PAT) principles in 2003 with the aim of building quality of the drug product right from the initial development stage [1]**.**The main objective of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the drug product [2]**.** In past decade, the traditional Quality by testing (QbT) approach was used to ensure the quality of drug products by checking it against the regulatory specifications. It is necessary to recognize that quality cannot be tested into drug products but it should be built in by design [3]**.** QbD is described in ICH Q8, Q9 and Q10 guidance documents. QbD principles promote systematic, scientific knowledge based development and continuous improvement of pharmaceutical drug products. Application of these guidance documents to pharmaceutical product development is depicted in Figure 1. By gaining the product/process knowledge, risk assessment and its management, quality management system along with the use of process analytical technology (PAT) tools for successful product development [4]

The real time release (RTR) testing concept was defined in USFDA PAT guidance document which offers some advantage i.e. increased process control and quality assurance, low analytical and material cost, low rejection and high yield [5]. The purpose of this study was to explore the design space during the development of immediate release tablets of Hydralazine hydrochloride, using elements of QbD and risk management. The disintegrant and lubricant level plays an important role and should be consider during the development of Hydralazine hydrochloride IR tablets.

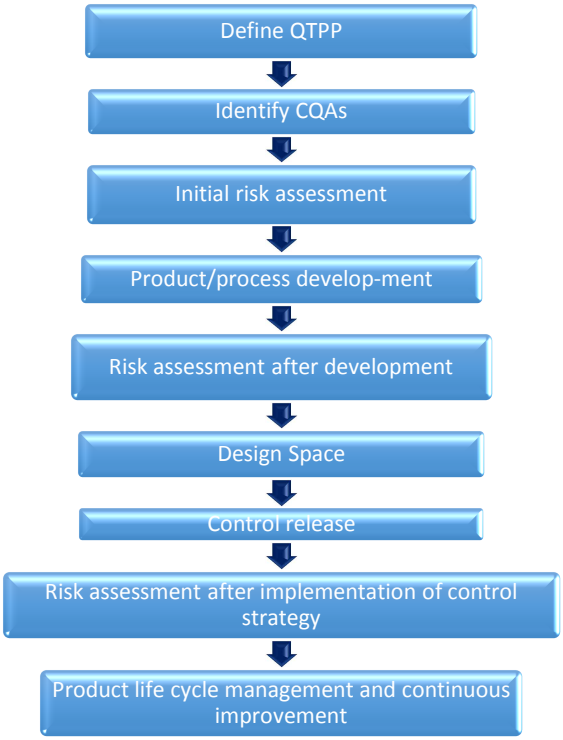

Figure 1 Quality by design, risk assessment and quality management in formulation development

EXPERIMENTAL SECTION

Materials

Hydralazine Hydrochloride API was gifted from IPCA Laboratory, India. Lactose anhydrous and monohydrate, maize starch, microcrystalline cellulose, dicalcium phosphate dehydrate, mannitol, pregelatinized starch, sodium starch glycolate, hydroxypropyl cellulose, crospovidone, cross carmellose sodium, colloidal silicon dioxide, talc, magnesium stearate, stearic acid was available in the School of Pharmacy, DAVV, Indore. All other chemical and solvent were of analytical grade.

Methods

QTPP (Quality Target Product Profile) and Critical Quality Attributes (CQA's):The USFDA guidance document provides the QTPP template, which describes the elements of QTPP for new drug applications and CQA template, identification of quality attributes of the drug product with proper justification [6]. QTPP elements and TPQP targets for IR hydralazine tablets are listed in Table 1 and 2.International conference of harmonization (ICH) Q8R2 guidance document describe the quality properties that a drug product should possess in order to achieve target set in QTPP elements are enlisted in target product quality profile (TPQP) as quantitative and qualitative attributes [7]. Quality target product profile (QTPP) should only include patient relevant drug product performance characteristics i.e. % friability, disintegration time, assay, dissolution, impurities etc.

Table 1. Preparation of QTPP

QTPP Elements	Target Product Quality Profile (TPQP)	Justification
Dosage form	Immediate release tablet	Pharmaceutical equivalence requirement
Route of administration	Oral	Same route of administration as Reference product
Dosage strength	100 mg	Pharmaceutical equivalence requirement
Appearance	Uncoated tablet	Similar to RLD.
% Friability	NMT 1.0%	Pharmaceutical quality standard requirements
Dissolution	NLT 75% Q in 45 min	Dissolution profile should match with RLD in OGD media
Assay	90-110%	Pharmaceutical quality standard requirements
Impurities	Single maximum unknown impurity: NMT 0.20% Total impurities: NMT 0.50%	Based on reference product evaluation and ICH requirements. Needed for clinical safety

Table 2. Identification of Critical Quality Attributes (CQA's)

Quality Attributes of the Drug product	CQA (Yes/No)	Justification
Appearance	No	Appearance is not directly linked to safety and efficacy. The target is set to ensure patient acceptability and to match reference product
Size	No	For patient acceptance and compliance with the regimens. The tablet dimensions are set close to reference product dimensions
Friability	Yes	Friability is critical and directly linked to the integrity during packaging and transport of the drug product. Drug product is uncoated tablets. Thus, friability will be monitored throughout product and process development
Identification	Yes*	Identification is critical for safety and efficacy but it will be effectively controlled by the quality management system. Formulation and process variables do not impact on Identity. Therefore, this CQA will not be discussed during formulation and process development
Assay	Yes	Variability in assay will affect safety and efficacy. Hence, process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development
Disintegration Time	Yes	Variability in disintegration time will affect drug release and finally bioavailability of formulation. Formulation and process variables can affect DT, thus it is critical and will be evaluated
Dissolution	Yes	Failure to meet the dissolution specification can impact bioavailability of the drug product. Both, formulation as well as process variables affects the dissolution profile. Hence, dissolution is critical and will be evaluated during formulation and process development
Impurities/Degradation product	Yes	The degradation product is critical for drug product safety. Hence, this CQA will be investigated throughout formulation and process development

Drug-excipients compatibility study: The various excipients were studied with the drug substance at accelerated temperatures and humidity condition to assess the compatibility of the excipients with the Hydralazine hydrochloride drug. The drug- excipients ratios were studied as similar to that which would be found in the final formulation. The drug excipient compatibility study was carried out for 1M at 40/75% RH condition. The samples were further analysed for impurities of drug substances using developed HPLC method.

Initial risk assessment, manufacturing design and development of tablets: An initial risk assessment for API and drug product/formulation are carried out to identify potential interaction between drug substance, excipients, various unit operations and key attributes [8].The quality risk management (QRM) concept was discussed in ICH Q9 [2] guidance document for identification, controlling, communicating and continuous monitoring the quality attributes of the drugs across product life cycle. Application of QRM process during development process of hydralazine IR tablets is discussed here. CQAs are derived from QTPP, prior knowledge and based on previous experience. Criticality of CQAs which is also known as risk, generally identified and rated(as high, medium, low) based on the potential of risk to the product. CQAs are physical, chemical, biological or microbiological property that should be addressed to ensure product quality, safety and efficacy [7-9].Direct compression is the easiest technique and was used for the preparation of Hydralazine IR tablet. The excipients were used similar to those used in the marketed formulation and quantities were based on the literature survey, previous experience and knowledge.

Experimental design: The design of experiment (DoE) is mathematical method for systematically planning and conducting experiments so that the data obtained can be analyzed to yield valid and objective conclusions. The components of experimental design are factors or inputs, levels and responses. Some commonly employed statistical techniques for design of experiments are factorial design, fractional factorial design, Placket – Burman [10]. Taguchi design, response surface design (Box- behnken and central composite design), mixture design (simplex – lattice and simplex – centroid design), combined design. Out of all of experimental designs, factorial and central composite designs have extensively been used to optimize pharmaceutical drug delivery systems [11].In the present study, three level two factor factorial designs were employed to know the interaction of all levels of a given factor with all levels of other factor studied [11]. Following study has been adopted to identify the design space of the investigated Hydralazine hydrochloride IR tablets.

The following physicochemical parameters were fixed for in process characterization of compressed tablets i.e. Tablet weight- 500 mg ± 5%, diameter-11.0 ± 0.1 mm, thickness- 5.0 ± 0.2 mm, hardness range- 90 to 120 N.

Study 1Effect of disintegrant and lubricant concentration on disintegration time and dissolution profile: Sodium starch glycolate is direct compressible grade of super-disintegrant which swell to 5-10 times within 30s [12]. Two factors factorial design at three levels consisting of nine runs was performed to study the impact of disintegrant and lubricant concentration on disintegration time and dissolution profile. The drug Hydralazine hydrochloride and various excipients were weighed in separate individual polybags as per the table 3 and sifted through suitable mesh size. The drug (100mg/tablet) and various excipients such as mannitol, sodium starch glycolate (SSG), colloidal silicon dioxide, magnesium stearate was mixed as per the table 3, in the suitable capacity blender (occupancy between 40-70 %) for the sufficient time period to ensure the homogenization and uniformity of the blend.

Table 3 Experimental trials

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydralazine Hydrochloride	100	100	100	100	100	100	100	100	100
Mannitol	377.5	377.5	377.5	377.5	377.5	377.5	377.5	377.5	377.5
FD&C yellow aluminium lake	5	5	5	5	5	5	5	5	5
Colloidal silicon dioxide (Aerosil 200)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Starch Glycolate	5	5	5	10	10	10	15	15	15
Magnesium stearate	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5

Study 2 Effect of blending time on blend uniformity: Blending time was identified as the most important process parameter that may affect tablet content uniformity. The blender speed was kept constant during complete mixing process. The sample for blend homogeneity were taken in triplicate from different ten locations (i.e. four samples from top layer, two samples from middle layer and four samples from bottom layer) as detailed in table 6, in blender using sampling thief. The samples were further analysed for blend uniformity/assay by HPLC method.

Study 3: Effect of lubrication time on disintegration time and dissolution profile: The effect of lubrication time on the disintegration time and dissolution profile was evaluated using one variable at a time (OVAT) technique. The optimized formulation was lubricated for 1 to 4 min.

RESULT AND DISCUSSION

Drug- excipients compatibility study: No interaction was observed in any of the excipients selected for the study. A compatibility study of drug substance with excipients is an early risk reduction strategy.

Study1. Effect of disintegrant and lubricant concentration on friability, disintegration time and dissolution profile: The disintegrant and lubricant concentrations were optimized using two factor three level factorial designs. The disintegrant and lubricant concentration were studied i.e. 1.0 %, 2.0%, 3.0% and 1.0 %, 1.5%, 2.0% w/w respectively, of tablet to study its impact on DT and dissolution of the drug product. The following trials were conducted to optimize the lubricant concentration and its impact on physical parameter discussed in table 4 and 5.

- Friability was found to be less than 0.5% for all the formulation studied and hence was not considered as a critical quality attribute.
- In experiments F1, F4 and F7- sticking and picking observed in tablets due to insufficient lubrication of blend. Hence, these trials were not further analyzed for dissolution and chemical impurities.
- In experiment F2- capping issue observed in tablets which was overcome by applying pre-compression force and tablet compressed. The tablets were not further analyzed for dissolution and impurities.
- In experimentsF8 and F9- higher level of disintegrant concentration with optimum and higher level of concentration both was not having significant impact on disintegration time and dissolution profile. The tablets were not further analyzed for chemical impurities and force degradation studies.
- In experiments F3, and F6- higher level of lubricant concentration with low and medium level of disintegrant both was retarding DT and release profile of tablets. The tablets were further analyzed for chemical impurities and force degradation studies.

Table 4. Various experimental trials (F1, F2, F4 and F7) with CQA's and physical observation

CQA's	F1	F2	F4	F7
Hardness (N)	90 - 112	91 - 114	90 - 115	93 - 118
% Friability	0.21	0.15	0.27	0.19
DT (minutes)	1 min 20s to 1 min 40s	1 min 25s to 1 min 50s	1 min 04s to 1 min 20s	55s to 1min 10s
Observation	Sticking and picking observed	Capping issue	Sticking &and picking observed	Sticking & picking observed

Table 5: Various experimental trials (F3, F5, F6, F8 and F7) with CQA's and physical observation

CQA's		F3	F5	F6	F8	F9
Hardness (N)		90 - 112	89 - 113	91 - 111	92 - 114	88 - 110
% Friability		0.19	0.20	0.27	0.11	0.23
DT (minutes)		1 min 27s to 1 min 58s	1 min 05s to 1 min 23s	1 min 18s to 1 min 39s	57s to 1 min 20s	1min to 1 min 35s
Dissolution	Time (min)	Media: 0.01N HCl, 900 ml, USP Type I apparatus, 100rpm				
	15	84.5	98.1	91.4	98.3	96.2
	45*	94.7	101.2	97.8	101.5	100.6
Observation		Slow disintegration and dissolution profile	Satisfactory physicochemical parameters	DT prolong and dissolution retard	No significant impact on DT and Dissolution profile	No significant impact on DT and Dissolution profile

**Q point = 45 minutes*

Study 2. Effect of blending time on blend uniformity: The average drug content in the blend was 96.53% (RSD = 4.73), 100.94% (RSD = 2.63), and 96.26% (RSD = 4.39) respectively at 10, 20 and 30 min time interval. Increasing the mixing time from 10 min to 20 min had a positive influence on blend uniformity {(blend assay 96.53%; RSD= 4.73) to (blend assay 100.94%; RSD= 2.63)}.The further increasing the mixing time from 20 min to 30 min, the % RSD was 4.39.Based on the following results, % RSD at 20 minutes blending time is less than 3.0%. Hence, 20 minutes dry mixing time is sufficient for efficient mixing of drug with different excipients.

Table 6: Optimization of blending time

S. No.	Sampling location	% Assay		
		10 minutes	20 minutes	30 minutes
1.	Top left (TL)	89.5	100.3	94.3
2.	Top right (TR)	95.2	98.9	97.1
3.	Top front	98.7	99.4	91.4
4.	Top back	95.3	103.5	102.3
5.	Middle left	102.4	97.7	89.7
6.	Middle right	99.6	105.1	97.2
7.	Bottom left	100.9	101.7	99.8
8.	Bottom right	89.7	100.6	100.5
9.	Bottom front	93.8	104.4	92.0
10.	Bottom back	100.2	97.8	98.3
Average		96.53	100.94	96.26
% RSD		4.73	2.63	4.39

Study 3. Effect of lubrication time on disintegration time and dissolution profile: Based on the following results as shown in table 4,DT of tablets was 1 min 7s to 1 min 24s, 1 min 5s to 1 min 23s and 1 min 3s to 1 min 28s respectively at after lubricating the blend for 1, 2 and 4 min. Hence, there is no significant impact on DT of tablets which was compressed at hardness range of 90-110 N and % drug release with lower and higher lubrication time of the lubricated blend. The pre-lubricated blend was lubricated using magnesium stearate before compression to reduce the friction in die cavity during ejection of tablets from the die cavity. Magnesium stearate is a hydrophobic lubricant which coats the granules [13].

Table 7. Optimization of lubrication time

Trial		F10	F5	F11
Lubrication time (min)		1	2	4
Hardness (N)		90 - 110	89 - 113	90 - 110
DT (minutes)		1 min 07s to 1 min 24s	1 min 05s to 1 min 23s	1 min 03s to 1 min 28s
Dissolution*	Time (min)	Media: 0.01N HCl, 900 ml, USP Type I apparatus, 100rpm		
	15 min	98.0	98.1	97.5
	Q point; 45 min	100.7	101.2	99.6

Design space and control strategy: The solubility, identification, particle size distribution, polymorphic form, related substance, residual solvent, residue on ignition, heavy metal contents are critical drug substance attributes. Thus, initial risk assessment of API is necessary but in this study all the attributes were well controlled by predefined specification.

CQAs of the drug product were identified by the initial risk assessment analysis and their relationship to critical material attributes/unit processes was established. The quality of the drug product was built within this space known

as “Design Space”. Design space should be wider for more robust and flexible process development to accommodate the variations. The design space was defined and listed out the methodology for describing design space for new processes where limited information was available. Design space boundaries are the basis of validation acceptance criteria [14]. The successful development and performance of drug product would generally depend on the execution of the plan, including control strategy and process monitoring [3].

The CQA’s derived from QTPP were linked to CMA’s and CPP’s. Compliance to disintegration time and dissolution profile is assured by using super-disintegrant amount (sodium starch glycolate), lubricant amount, blending time and lubrication time within design space.

CONCLUSION

Quality by design approach is a systematic tool for manufacturing and continuous improvement of quality of Hydralazine IR Tablets. Various other approaches such as six-sigma, lean manufacturing program and process capability measurement can also be adopted. Disintegrant and lubricant concentrations were identified as the two critical materials attributes for achieving goals set in TPQP. Similarly, blending and lubrication time were selected as critical process attributes to achieve the blend homogeneity. Operating within the design space provided the robustness, flexibility in manufacturing, manufacturer confidence and quality drug products to the patient and society.

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