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Quality by design approach for formulation development: A case study of dispersible tablets☆

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ABSTRACT

The focus of the current investigations was to apply quality by design (QbD) approach to the development of dispersible tablets. Critical material and process parameters are linked to the critical quality attributes of the product. Variability is reduced by product and process understanding which translates into quality improvement, risk reduction and productivity enhancement. The risk management approach further leads to better understanding of the risks, ways to mitigate them and control strategy is proposed commensurate with the level of the risk. Design space in combination with pharmaceutical quality management system provide for flexible regulatory approaches with opportunity for continuous improvement that benefit patient and manufacturer alike. The development of dispersible tablet was proposed in the current study through a QbD paradigm for a better patient compliance and product quality. The quality target product profile of a model biopharmaceutical class II drug was identified. Initial risk analysis led to the identification of the critical quality attributes. Physicochemical characterization and compatibility studies of the drug with commonly used excipients were performed. Experiments were designed with focus on critical material and process attributes. Design space was identified and risk factors for all the possible failure modes were below critical levels after the implementation of control strategy. Compliance to the design space provides an opportunity to release batches in a real time. In conclusion, QbD tools together with risk and quality management tools provided an effective and efficient paradigm to build the quality into dispersible tablet.

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1. Introduction

The Federal Food and Drug Act known as Wiley Act was signed into law by the President Roosevelt in June 1906 (Food and Drugs Act of 1906). The act made it illegal to manufacture and ship adulterated and misbranded drugs. The Federal Food, Drug and Cosmetic Act of 1938 added the requirement for preapproval of drugs before marketing them (Janssen, 1981). In 1962, amendments (Federal Food, Drug and Cosmetic Act 1962) were made to add the requirement for effectiveness and comprehensive safety testing. Hatch-Waxman (Rosen, 2005) reform in 1984 authorized the marketing of generic versions of the originator drug upon approval of Abbreviated New Drug Application (ANDA). In its initiative for the 21st century Good Manufacturing Practice (Food and Drug Administration, 2003), FDA initiated quality by design (QbD) and process analytical technology (PAT) principles in 2003 with the purpose of building quality into the product right from the beginning of manufacturing (Food and Drug Administration, 2006). The traditional quality by testing (QbT) approach tests product quality by checking it against the approved regulatory specifications at the end of manufacturing stream at great effort and cost. There is a great deal of unpredictability in scaling up a product from research and development to production scale and reasons for failure are generally not understood. Failure of products to comply with their specifications would amount to either rejection of the batch or reworking of the batch with increased cost and regulatory burden. Post approval changes even of noncritical nature will need preapproval by the regulatory authorities. For critical products, the wastage of a batch can be challenging for a pharmaceutical company in terms of sustaining the market competition. Thus lack of product and process understanding results in a wide

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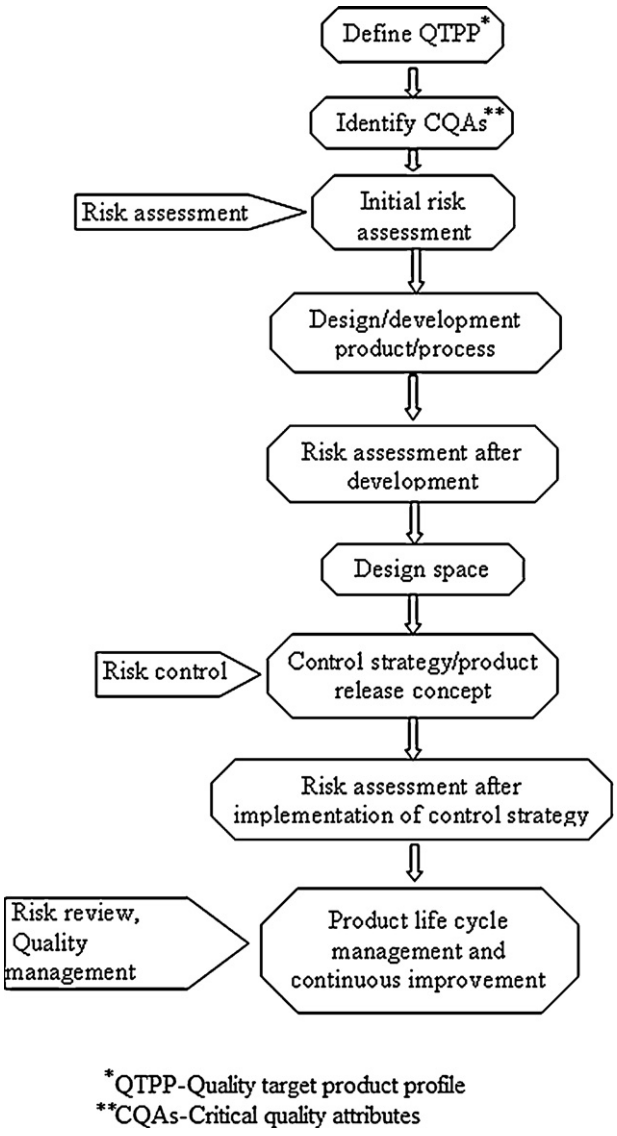

Fig. 1. QbD, risk management and quality management in formulation development.

communication gap between regulatory bodies and the manufacturing companies which underscores the need for intensive regulatory oversight.

QbD is also described in ICH Q8 (Food and Drug Administration, 2006), Q9 (ICH, 2005) and Q10 (ICH, 2008) guidance documents and is a major shift from the traditional approach of QbT in ensuring quality control of products across the manufacturing stream. QbD principles promote innovation and continuous improvement of the product. Knowledge based commercial manufacturing ensues enough regulatory flexibility for setting specifications and post approval changes. Product and process are designed using innovative risk based techniques to meet predefined quality objectives thereby satisfying the most critical patient needs and regulatory requirements at low cost. Application of these guidance documents to product development is depicted in Fig. 1. The purpose of this study was to explore the design space during the development with a pre-designed quality of a robust and stable dispersible tablet of a BCS class II analgesic drug, namely diclofenac, using elements of QbD and risk management. Dispersible tablets offer an advantage in administration of drugs to pediatric, geriatric and dysphagic patients. Further, the quick absorption provides fast relief in pain associated with rheumatoid arthritis, tooth ache, back ache, etc. The fast disintegration of such tablets (disintegration time < 3 min) (British Pharmacopeia Convention, 2009) is essential for their rapid dispersion which is achieved usually by using high level of disintegrants in the formulation and by compressing them at comparatively lower hardness as compared to the conventional tablets. The lower hardness and high disintegrant level demand careful handling of tablets subsequently during packaging and shipping. Also the packaging should be strong enough to protect the integrity of dosage form during the shelf life.

2. Materials and methods

2.1. Materials

Diclofenac was purchased from Sureka Pharma (Madhya Pradesh, India). Microcrystalline cellulose (Patel Industries, Ahmedabad, India), croscarmellose sodium (Signet Chemical Corporation, Mumbai, India), crosspovidone (Guzhou Jianhua Nanhang Industrial Co. Ltd., China), sodium starch glycollate (Maple Biotech Pvt. Ltd., Pune, India), talc (Neelkanth Healthcare Pvt. Ltd. Mumbai, India) and magnesium stearate (Faci Asia Pacific PTE LTD, Singapore) were USP grade. All other chemicals and solvents were of analytical grade. JMP® (SAS Campus Drive, Building T, Cary, NC, 27513) software was used to analyze the data and generate graphs. Figs. 9 and 10 were drawn using Design Expert® software.

2.2. Methods

2.2.1. Target product profile (TPP) and quality Target product profile (QTPP)

TPP embodies the overall objectives of safety and efficacy of a drug development program and thus links the latter to the drug labeling (Delasko et al., 2005) to make the generic product development program patient oriented. The primary components of TPP are mainly clinical pharmacology aspects such as indications, side effects, route of administration, dose, etc. For a generic drug product, the TPP is same as the innovator product and can be easily derived from the innovator product labeling. Each labeling concept is based on the specific clinical study undertaken by the innovator for the new drug products. The US FDA guidance document provides the template TPP, which describes the components of TPP for new drug applications. (Food and Drug Administration, 2007). TPP and QTPP for dispersible tablet dosage formulation are listed in Table 1. The quality properties that a drug product should possess in order to meet objectives set in TPP are enlisted in target product quality profile (TPQP) as quantitative attributes (Lionberger et al., 2008). Lionberger et al. (2008) emphasized the need for distinction between TPP and TPQP which is quantitative surrogate for the clinical safety and efficacy (Lionberger et al., 2008). However, International conference of harmonization (ICH) Q8R2 (Food and Drug Administration, 2009) summarizes them as QTPP. QTPP lays the foundation for formulation/process design and it should only include patient relevant product performance characteristics such as assay, content uniformity, dissolution, impurity profiling, stability, etc.

2.2.2. Manufacturing design and development of dispersible tablets

An initial risk assessment is carried out to identify potential interaction between drug, excipients, various unit operations and key attributes. Risk based compliance is an important FDA initiative for current Good Manufacturing Practice (cGMP) for the 21st century (Food and Drug Administration, 2003). ICH Q9 (ICH, 2005) guidance document introduced the concept of quality risk management for assessing, controlling, communicating and reviewing risks to the quality of drugs across product life cycle. The emphasis

Table 1
TPP and QTPP for a generic dispersible tablet dosage form.

Attribute	QTPP		Criticality
	TPP	TPQP	
Dosage form	Dispersible tablet	DT (<3 min), dissolution (not less than 85%(Q) in 30 min in pH 6.8 buffer medium)	Ensures complete dispersion, release of drug, efficacy and ease of administration
Appearance	Uncoated tablets	IR round tablets	Patient acceptability and compliance
Strength	46.5 mg	Identification (positive), Assay (±5%), content uniformity (complies)	Efficacy
Route of administration	Oral	Palatable	Patient compliance to therapy
Proposed indications	Treatment of pain associated with arthritis	Dissolution and bioequivalence	Ensure therapeutic efficacy
Impurities	–	Qualified to meet ICH Q3B and Q6A criteria	Safety is assured by controlling any impurity at NMT 0.2% and total impurities at NMT 0.5%. Limit has been qualified in toxicological studies.

is on knowledge based evaluation of the risk to the patient (QTPP) and effort to reduce the risk in commensurate with level of the risk. The components of a quality risk management process are: (i) risk assessment (it includes risk identification, risk analysis and risk evaluation); (ii) risk control (it includes risk reduction and risk acceptance); (iii) result of the quality risk management process; and (iv) risk review.

Application of quality risk management process in the development of a dispersible tablet dosage form is provided in the following discussion. During the risk assessment, the key properties called critical quality attributes (CQAs) that could vary during various manufacturing unit operations were identified. CQAs are physical, chemical, biological or microbiological property or characteristics that should be within an established range to ensure product quality, safety and efficacy (ICH, 2008; Glodek et al., 2006). Critical material attributes (CMAs) are used for the attributes of drug substance, excipients and in process materials. CQAs are derived from QTPP and prior knowledge. During the development stage as the knowledge of product and process increases the potential CQAs also evolve. The risk identification is qualitatively evaluated by the product development team using risk management tools like such as Failure Mode Effects Analysis (FMEA), Fault Tree Analysis (FTA) (US Food and Drug Administration/US Department of agriculture 1997), Hazard Analysis and Critical Control Points (HACCP) (WHO Technical Report, 2003; British standard BS), Hazard Operability Analysis (HAZOP) (British standard BS, 2002), Preliminary Hazard Analysis (PHA) (Ericson, 2005), Risk Mapping, Failure Mode Effects and Criticality Analysis (FMECA) (International Society for Pharmaceutical Engineering, 2010; Haimes et al., 2002), Risk Ranking and Filtering (Haimes et al., 2002), etc. The objective is to find the harmful event, its cause, probability of occurrence, its impact and detection ability. The risks are rated (as high, medium, low or on a scale of 1–10) based on the potential of risk to the product. Risk priority number (RPN) is generated for all the critical events and events with high RPN number are attended first. Table 2 lists the initial risk assessment of dispersible tablets of a low soluble/high permeable drug (BCS class II) using PHA (Ericson, 2005). Quality attributes and likely hazards (API, excipient and process attributes) were selected from QTPP, preformulation studies and previous experience of working with similar dosage formulations. Severity of the hazard and Probability of occurrence were scored and risk ranking was performed as given by Hiyama (Hiyama, 2009). Direct compression is the easiest of available processes and was considered best for this dosage form. Particle size of the drug could affect bioavailability of BCS class II drug, flow properties of final mix and content uniformity. The diluent selected should be freely flowable for the direct compression process and should either aid in disintegration or not interfere with the disintegrant action. Manufacturing process should ensure quick disintegration and uniformity of dosage units of tablets. Being a dispersible tablet dosage form, lubrication level, lubrication time and hardness-window has to be defined as disintegration time (DT) is sensitive to these parameters. Initial literature search and preformulation studies revealed that drug is sensitive to moisture and hence packaging must be robust to protect the product (Fig. 2). Further, the drug handling and manufacturing should be carried out in environment below 60% RH.

The design of a discriminatory dissolution method could be an indicator for in vivo performance of the drug. The diclofenac has a very low solubility below pH 6 which was confirmed by very low drug release whereas above pH 6.8 it is highly soluble (Chuasuwan et al., 2009) and hence 900 ml pH 6.8 phosphate buffer was selected as the dissolution medium. The agitation speed of 75 rpm was found suitable for carrying routine quality control testing and provided the potential for discrimination among tablet variants. A biowaiver monograph based on above dissolution medium for diclofenac dosage forms has been published (Chuasuwan et al., 2009). Though the salt forms of diclofenac are highly soluble above pH 6.0, they are non palatable and cause irritation to throat when taken in the form of dispersion. Hence free acid was considered for the study. API manufacturer's quality system and control strategy ensured compliance to purity, residual solvent, moisture and stability specifications. Microcrystalline cellulose (MCC), croscarmellose sodium (CCS), crospovidone, sodium starch glycollate (SSG), talc and magnesium stearate were selected for preparing dispersible tablet dosage form. The initial selection of excipients was based on the experience with similar dosage forms, desired characteristics of the dosage form and knowledge of degradation mechanism such as interaction of amines with lactose (David et al., 1998). Microcrystalline cellulose was selected as the filler because of its good flow, direct compressible characteristics and disintegration properties due to the wicking action.

Moreover, similar excipients have also been used in marketed dosage formulation of diclofenac dispersible tablets, "Voltarol" tablets (Votarol, Summary of product characteristics, 2011). This will facilitate the biowaiver of diclofenac dispersible tablets as one of the many criteria for getting biowaiver for such a dosage form

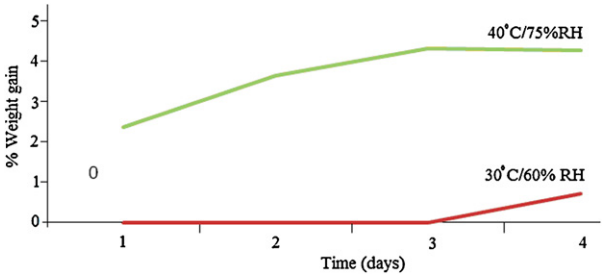

Fig. 2. Weight gain of drug stored at different conditions.

Table 2
Risk assessment by PHA to identify variables affecting drug product quality.

Quality attributes	Effect of API attribute on drug product quality							Effect of excipients on drug product quality					Effect of unit operations on drug product quality			
	Salt form	Particle size	Solubility	Stability	Purity	Residual solvent	Moisture	Microcrystalline cellulose	Croscarmellose sodium	Sodium starch glycollate	Magnesium stearate	Mixing	Lubrication	Compression	Packaging
Appearance	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Identification	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Microbiology	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Disintegration time	–	–	–	–	–	–	–	++	++	++	++	–	++	++	–
Dissolution	–	++	++	–	–	–	–	–	++	++	++	–	++	++	–
Hardness	–	–	–	–	–	–	–	–	–	–	+	–	++	++	–
Assay	–	–	–	–	++	–	–	–	–	–	–	++	–	–	–
Content uniformity	–	++	–	–	–	–	–	++	–	–	–	++	–	++	–
Flow	–	++	–	–	–	–	+	++	–	–	–	–	–	–	–
Taste	++	–	++	–	–	–	–	–	–	–	–	–	–	–	–
Degradation	–	–	–	–	–	–	–	–	–	–	–	–	–	–	++
Impurities	–	–	–	++	++	++	++	–	–	–	–	–	–	–	–

(–) low, (+) medium; and (++) high. API: active pharmaceutical ingredient.

is that the excipients present in test product are selected from diclofenac products approved in ICH or associated countries in the same dosage form (Chuasuwan et al., 2009).

A compatibility study of drug–excipient was performed. Drug was triturated with individual excipients in 1:1 ratio with and without water (%). The samples were stored for 4 weeks at 40 °C/75%RH and 30 °C/65% RH, analyzed for drug content and impurities using stability indicating HPLC method (U.S. Pharmacopeial Convention, 2007). No interaction was observed in any of the excipients selected for the study. A compatibility study of drug with excipients is an early risk reduction strategy which precludes the use of excipients which may interact with the drug substance.

2.2.3. Experiments designs

Fisher devised experimental design principles were used which have found applications in many areas including pharmaceutical development (Fisher, 1926). Pharmaceutical product development is designed to yield maximum knowledge of product performance systematically over a wide range of material and process attributes. Some commonly used experimental designs are factorial design (Armstrong, 1998), sequential simplex technique (Plackett and Burman, 1946), Placket–Burman (Armstrong, 1998; Plackett and Burman, 1946), Box–Behnken response surface methodology (Armstrong, 1998), D and I optimal techniques (Armstrong, 1998). The major benefit of using factorial design is that all estimated effects and interactions are independent of effects of other factors. Followings are the different studies that have been adopted to define the design space of the investigated dispersible tablets.

2.2.3.1. Study 1: effect of drug particle size and microcrystalline cellulose on flow characteristics, disintegration time and dissolution. A two factorial experiment at two levels with four run was carried out to find the effect of microcrystalline cellulose level (190, 220 mg per tablet) and drug particle size ($d(90) < 250\ \mu m$, $d(50) < 180\ \mu m$; $d(90) < 50\ \mu m$, $d(50) < 10\ \mu m$) on disintegration time (DT), flowability and dissolution. Different batches (batch size: 1.5 kg) were prepared by blending microcrystalline cellulose with the drug (46.5 mg/tablet), sodium starch glycollate: crosscarmellose sodium: (2.2:1) for 10 min followed by 3 min lubrication with 1% (w/w) magnesium stearate in 5 kg double cone blender. The blend was compressed at 50–60 N hardness in 10 station tablet compression machine (Anchor Mark, Mumbai, India) run at 35 rpm. The dissolution was performed in pH 6.8 phosphate buffer and absorbance of drug was read at 276 nm by UV spectrophotometry (U.S. Pharmacopeial Convention, 2007).

2.2.3.2. Study 2: effect of superdisintegrants and tablet hardness on disintegration time and friability. Croscarmellose sodium and sodium starch glycollate are super disintegrants which swell to 5–10 times in less than 30 s and are directly compressible (Shangraw and Demarest, 1993). The formulations were prepared with a constant drug particle size material ($d(90) < 250\ \mu m$, $d(50) < 180\ \mu m$). Three factors factorial design at two levels (sodium starch glycollate (SSG): croscarmellose sodium (CCS): 1.5:0; 1.5:1; 2.2:0; 2.2:1 and hardness: 40 N, 60 N) comprising of eight runs was performed to study the impact of disintegrants and tablet hardness on DT and friability. Microcrystalline cellulose (220 mg/tablet) was blended with drug (46.5 mg/tablet) and disintegrants in 5 kg double cone blender for 10 min (rpm). The blend was lubricated for 3 min with 1% magnesium stearate followed by compression in 10 station compression machine (Anchor Mark, Mumbai, India) at 35 rpm.

2.2.3.3. Study 3: effect of lubricant level on disintegration time and dissolution. Magnesium stearate is a hydrophobic boundary lubricant and has a tendency to increase disintegration time of tablets at

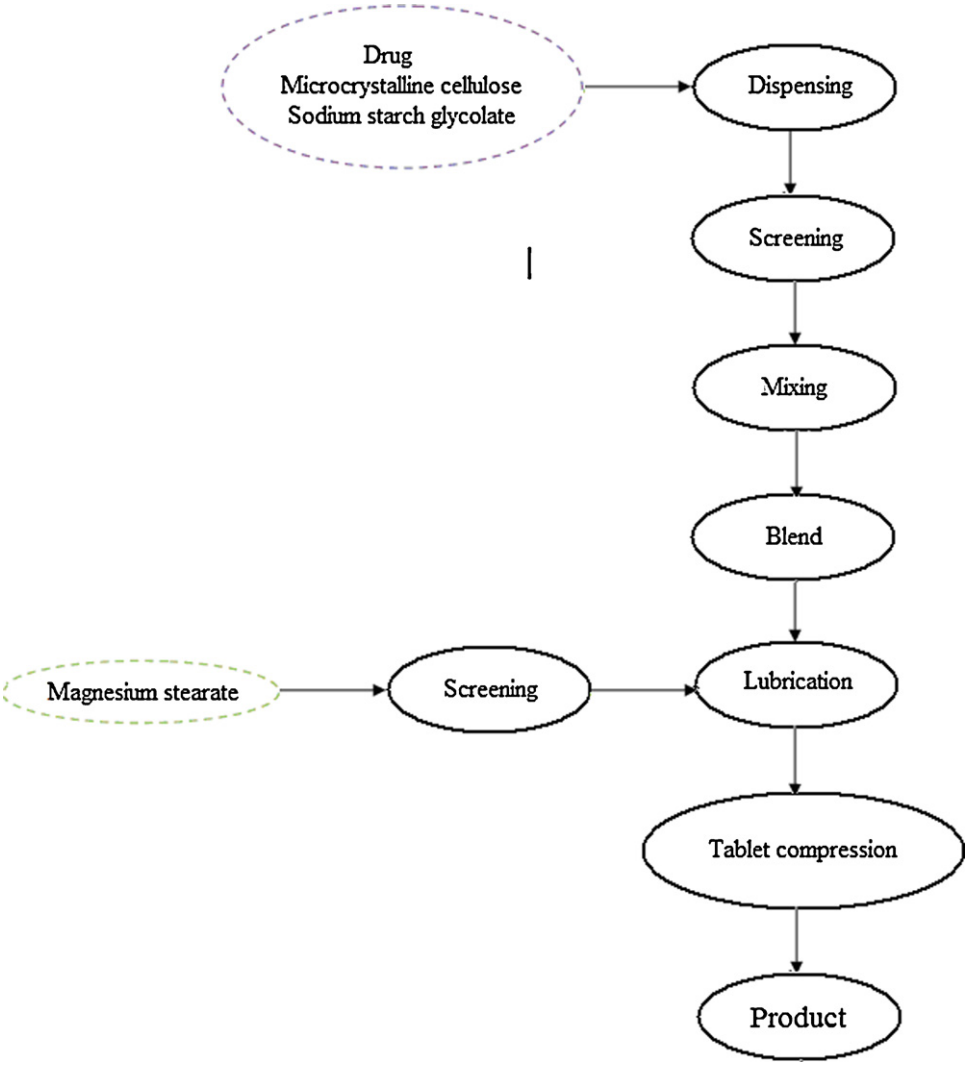

Fig. 3. Process flow diagram of orally dispersible tablet.

higher concentration and is sensitive to the mixing time (Hussain et al., 1990). The effect of magnesium stearate on disintegration time and dissolution was studied at 0.5%, 1.0% and 1.5% levels. The SSG and CCS were used in 1.5:1 (mg/tablet) ratio in the formulations. The other excipients and process parameters were same as in study 2.

2.2.3.4. Study 4: effect of packaging material on the stability. One batch of tablets was prepared with MCC (220 mg/tablet), SSG:CCS (1:2.2), magnesium stearate (0.5%) and packaged in two different packs namely polyvinylchloride (PVC) and polyvinylchloride/polyvinyldiene chloride (PVC/PVDC) by thermoforming in automatic blister packaging machine (Elmac, Mumbai, India). The process parameters were similar to the study 2. Both the packs were kept in stability chamber at 40 °C/75% RH for three months. The samples were withdrawn at definite intervals and analyzed for impurities by HPLC (U.S. Pharmacopeial Convention, 2007).

2.2.3.5. Study 5: risk analysis of critical process parameters. Risk analysis and assessment was performed by FMEA for identifying the critical process parameters. Definitions of RPN were same as provided by Hiyama (Hiyama, 2009). The process flow for manufacturing dispersible tablets is shown in Fig. 3.

2.2.3.6. Study 6: effect of blending process on blend homogeneity. Based on the preliminary investigations, the mixing time and compression machine speed were identified as the most important process parameters that can affect tablet content uniformity (Table 2). A three factorial experimental design ($2 \times 2 \times 3$) was performed to study the effect of mixing time (10, 15, 20 min), mixer speed (6 rpm, 12 rpm) and particle size ($d(90) < 250\,\mu m$, $d(50) < 180\,\mu m$; $d(90) < 50\,\mu m$, $d(50) < 10\,\mu m$) on blend homogeneity at 50% utilization of blender working capacity. The blend homogeneity was determined by dispersing the blend in pH 6.8 phosphate buffer and recording the UV absorbance of the drug at 276 nm. The samples for blend homogeneity were taken in triplicate from six different locations (top, middle and bottom layers) across the blender using sample thief. The formulation composition and process parameters were same as mentioned in study 2 with SSG and CCS in 1.5:1 ratio in the formulations. Downstream compression process further contributed to the blend non-homogeneity due to the intensive vibrations set in the compression machine. Therefore the blend uniformity was controlled at lower RSD (<3%) with target drug assay between 95 and 105% of the label claim to compensate for further de-mixing in the compression machine.

2.2.3.7. Study 7: effect of lubrication time on disintegration time. The effect of lubrication time at different levels of the lubricant on the DT was investigated in an experimental design comprising of eight runs. Magnesium stearate level varied from 0.5% to 1.5% while the lubrication time varied from 3 to 5 min. The composition of formulation and process parameters were same as in study 6. The double cone blender was operated at 12 rpm.

2.2.3.8. Study 8: effect of tablet compression process on CQAs. Based on preliminary investigations, the compression force and speed of the tablet press were identified as critical process attributes which can affect CQAs such as appearance, hardness, friability, dissolution, content uniformity and disintegration time (Table 2). Experiments comprising of nine runs were carried out at two different machine speeds (36×10^3 and 72×10^3 tablets per hour) and various compression forces on one batch prepared with 1.0% magnesium stearate. Content uniformity during the tabletting operation was controlled by in-process tablet weight checks at regular intervals. Samples across 20 locations during compression were taken and three tablets out of seven tablets per location were analyzed for drug content by UV spectrophotometer at 276 nm using pH 6.8 phosphate buffer as the diluent. A 7.5 kg batch with SSG and CCS in 1.5:1 ratio in the formulation was blended in 25 kg double cone blender with drug and other excipients used in same amount as in study 2. The blend was lubricated followed by compression in 10 station compression machine (Anchor Mark, Mumbai, India).

3. Results and discussion

3.1. Formulation and process development

The better process understanding and control are vital to minimize the product waste due to manufacturing failure and produce product of desired quality with reduced end product testing. These objectives were accomplished by identifying process variables for preparing robust diclofenac dispersible tablets, measuring and monitoring them as provided in process analytical technology (PAT) guidance document (Food and Drug Administration, 2004). PAT was introduced by US FDA to promote implementation of new technologies to the manufacturing process for achieving quality objectives by designing, analyzing and controlling manufacturing processes through timely measurements (i.e. on-line or in line) of critical process parameters that affect CQA. In the process development of diclofenac dispersible tablets, the effects of unit operations were related to the CQAs by risk assessment. Subsequent process development studies confirmed the criticality of the process parameters. Critical process parameters are the process inputs that when varied beyond the proven acceptable ranges (PAR), significantly affect the CQA therefore they must be controlled within predetermined limits (International Conference of Harmonization, 2000). PAR for a process parameter represents the process knowledge area and encompasses the region between the maximum and minimum value within which a product of predetermined quality is produced consistently. Large space certainly provides lot of regulatory flexibility to the sponsor however it comes with increased pharmaceutical development cost incurred in establishing this wide range. A wide range will minimize chances of operating outside the proven range and may reduce the risk of process parameter. For critical processes parameter, the normal operating range is typically close to PAR and/or it may interact with other parameters in this range. The sensitivity of process parameter was established by extensive process development studies that helped to mitigate the risk to the dispersible tablets by designing the knowledge based control strategy. Investigators (Lionberger et al., 2008) listed four categories for each unit operation in a process namely; input material attribute, output material attribute, input operating parameters and output process state conditions. The criticality of an unclassified parameter was undetermined or unknown and as the process understanding increased the unclassified process parameter might be categorized as critical or non critical. Menard (Menard, 2006) listed typical solid dosage form unit operations, process parameters and the quality attributes.

3.1.1. Study 1: effect of drug particle size and microcrystalline cellulose on flow characteristics, disintegration time and dissolution

The DT for all the four runs was between 50 and 60 s (Fig. 4A). No significant difference in disintegration time was observed in all the runs. The percentage compressibility index was determined as per Carr's method (Carr, 1965). The value of 20% or more indicates poor flow characteristics of a powder and formation of bridges in the hopper. The % compressibility was 18 when both the factors, i.e. drug particle size ($d(90) < 50$, $d(50) < 10\,\mu m$) and MCC (190 mg) were present at lower levels (−1, −1 factorial levels in Fig. 4B). Increase in either drug particle size (1, −1 factorial level) or MCC concentration (−1, 1 factorial level) resulted in lowering of % compressibility values to 13 and 10, respectively. The value decreased to 7.5% when both the factors were present at higher levels ($d(90) < 250\,\mu m$, $d(50) < 180\,\mu m$, 220 mg) indicating excellent flow properties of the blend. This was further confirmed by the low variability (RSD < 1.5) for blends prepared with higher level of microcrystalline cellulose (Fig. 4D). The effect of smaller drug particle size on the compressibility index was evident and was compensated by higher level of microcrystalline cellulose. Similarly, as shown in Fig. 4C, the dissolution profile of the drug for two particle size materials determined by spectrophotometry using paddle apparatus at 75 rpm was similar ($p > 0.05$) and hence the effect of drug particle size on dissolution after 30 min in 900 ml pH 6.8 phosphate buffer was insignificant. However, both drug particle size and MCC when used in higher level significantly ($p < 0.05$) reduced drug release to 97%. Microcrystalline cellulose being insoluble may have negative influence on the dissolution when used at very high concentration. However this did not warrant attention as the drug release was above 95%, and the nature of dosage form ensured faster and complete dissolution rate.

3.1.2. Study 2: effect of superdisintegrants and tablet hardness on disintegration time and friability

As shown in Fig. 5A, DT of formulations at 40 N was 270 s when both the disintegrants were used at lower concentration levels (SSG:CCS; 1.5:0). On increasing the SSG level (SSG:CCS; 2.2:0), DT was significantly ($p < 0.05$) reduced to 157 s. With other two factors at their lower levels, higher level of CCS (SSG:CCS; 1.5:1 at 40 N hardness) produced more pronounced effect on DT (65 s, $p < 0.05$). The DT at hardness of 40 N was further reduced to 34 s ($p < 0.05$) in formulations containing both disintegrants at their higher level (SSG:CCS; 2.2:1) and on increasing hardness to 60 N, the DT increased to 60 s but was well below the target value of 120 s (British Pharmacopoeial limits for DT < 180 s) (British Pharmacopeia Convention, 2009). Friability was found to be below 0.5% for all the formulations studied and hence was not considered as critical. It can be seen from the contour plot in Fig. 5B that tablets with DT of less than 120 s can be made in large area of the design space and various combinations of disintegrants and hardness will satisfy the requirement.

3.1.3. Study 3: effect of lubricant level on disintegration time and dissolution

Fig. 6 shows that the effect of magnesium stearate on disintegration time and dissolution was found insignificant ($p > 0.05$) at 0.5–1.5% concentration. Hydrophobic lubricants such as

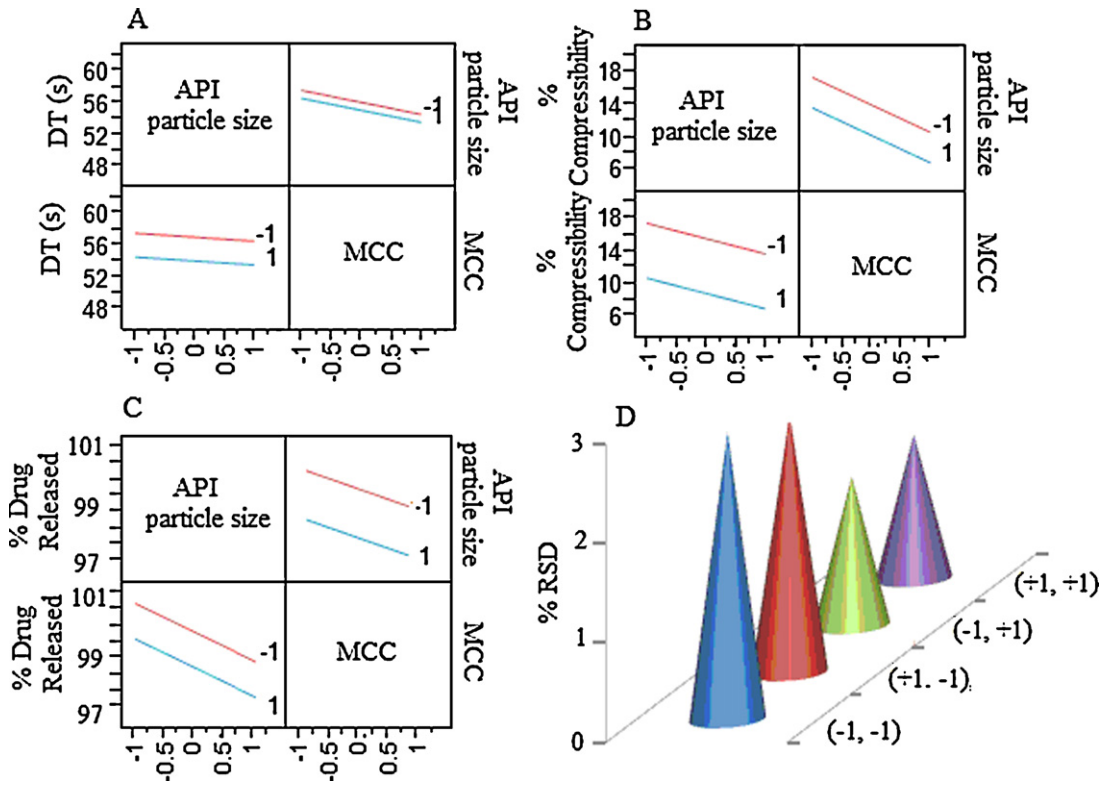

Fig. 4. Interaction profiles showing the effect of drug particle size and microcrystalline cellulose concentration on (A) DT, (B) % compressibility, (C) dissolution profile and (D) %RSD.

magnesium stearate form a coat around the granules which might lead to an increase in DT and a decrease in the dissolution rate. Their presence might also result in loss of cohesive forces due to interference with particle–particle bonding and weaker tablets are produced.

3.1.4. Study 4: effect of packaging material on the stability

The dispersible tablets need careful handling and protection from moisture. The packaging must be robust enough to protect tablet integrity throughout the shelf life as ingress of moisture may initiate disintegration process. The formulation packed in PVC/PVDC showed better stability characteristics than PVC after 3 months of storage time (Fig. 7). The increase in % total impurities after 3 months of storage at accelerated conditions were significantly lesser ($p < 0.05$) in formulations which were packaged in PVC/PVDC (0.1%) than the formulations packaged in PVC alone (0.23%). PVDC increased the barrier properties of standard PVC film several folds due to the decrease in water vapour transmission rate (Banker et al., 1966). The additional protection due to PVDC coating on PVC prevented moisture increase and improved the stability performance of the dosage form significantly. Hence, PVC/PVDC was selected as the packaging material for packaging diclofenac dispersible tablets.

3.1.5. Study 5: risk analysis of critical process parameters

Mixing time, lubrication and compression force might affect CQAs significantly. As shown in Fig. 4, the effect of particle size of drug and microcrystalline cellulose on blend homogeneity was

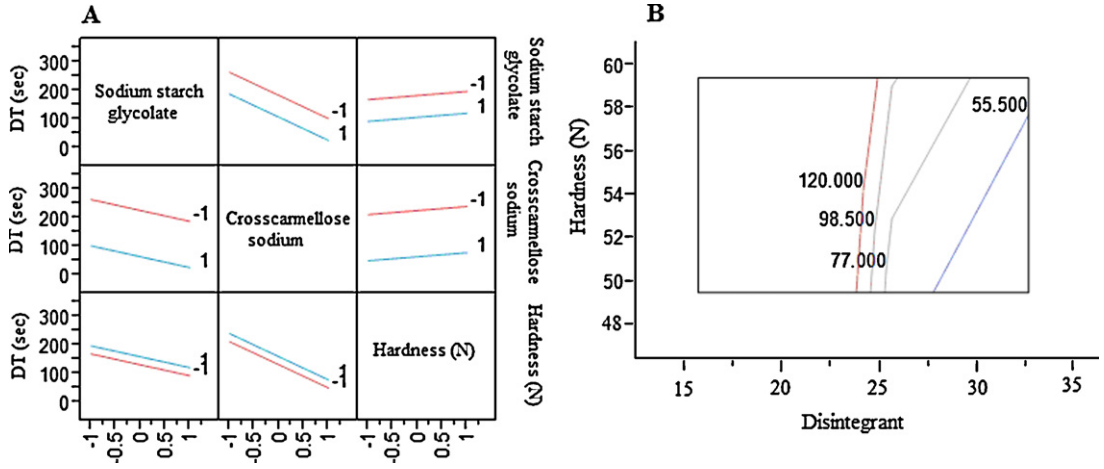

Fig. 5. (A) Interaction profile for DT with varying disintegrant concentration and hardness and (B) contour plot of DT as a function of disintegrant concentration and hardness.

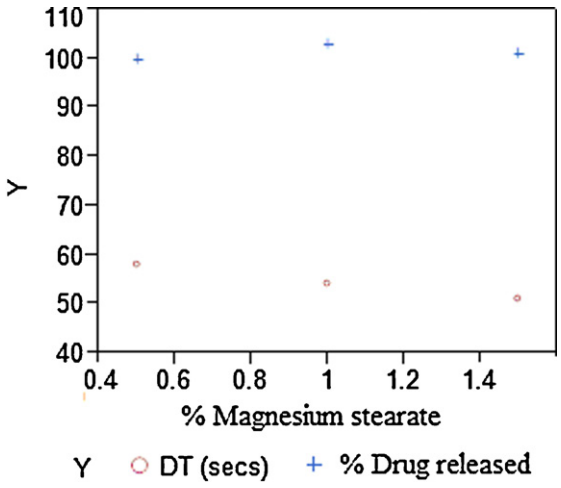

Fig. 6. Overlay plot showing effect of magnesium stearate on DT and dissolution.

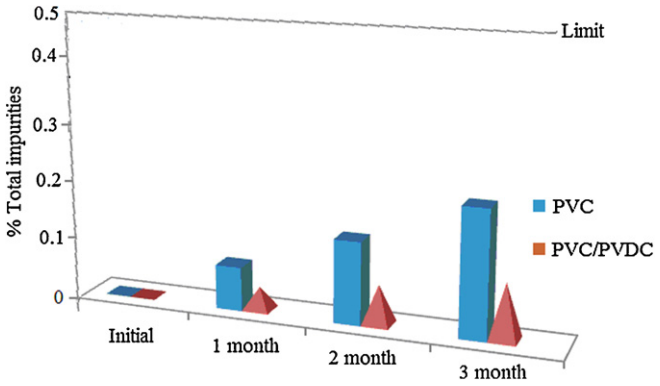

Fig. 7. Effect of packaging materials on drug degradation.

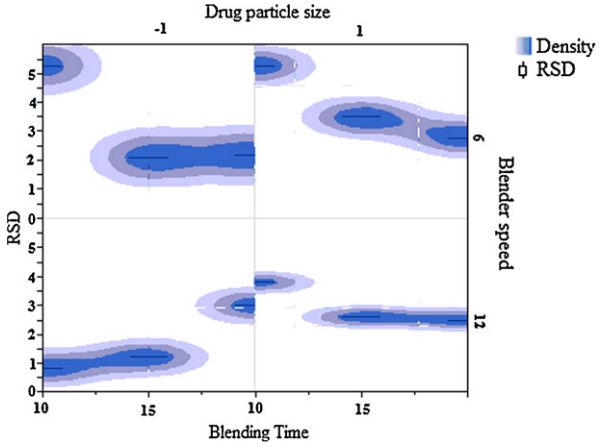

Fig. 8. Effect of blending process on blend homogeneity.

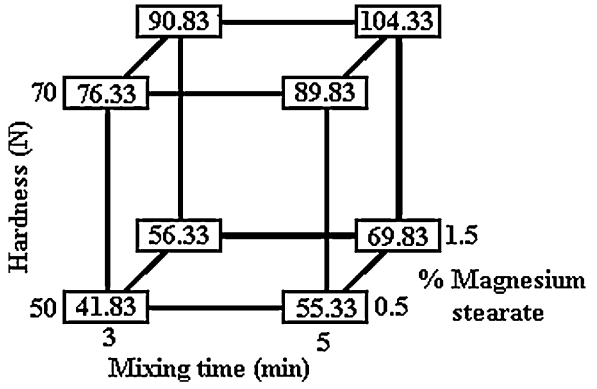

Fig. 9. Effect of lubrication time on DT.

evaluated and a controlled strategy was designed to further reduce the risk to blend homogeneity. Table 2 shows that the mixing time and rotation speed of the compression machine were the most important process parameters that affected the content uniformity. Homogeneity of the blended powder at different blender time and speed utilizing 50% working capacity of the double cone blender was assessed by UV spectrophotometry. Downstream compression process further contributed to the blend non-homogeneity due to the intensive vibrations in the compression machine. Therefore, the blend uniformity was controlled at lower RSD (<3%) to compensate for further de-mixing in the compression machine.

3.1.6. Study 6: effect of blending process on blend homogeneity

As depicted in Fig. 8, after 10 min of mixing at 6 rpm, the % average drug content in the blend was 94% (RSD = 5.3) with higher particle size drug which improved slightly to 97% (RSD = 5.3) when smaller particle size drug was used. Increasing the mixing time to 15 min at 6 rpm had a positive influence on blend uniformity in formulations with smaller drug particle size (blend assay 100%; RSD = 2.1) and larger drug particle size (blend assay 98%, RSD 3.5), respectively. On increasing the speed of blender to 12 rpm, the % average drug content in the formulations was 103% (RSD = 0.8), 100% (RSD = 1.2) and 99% (RSD = 3%) respectively at 10, 15 and 20 min with lower drug particle size. The blends with smaller drug particles showed comparatively better homogeneity with

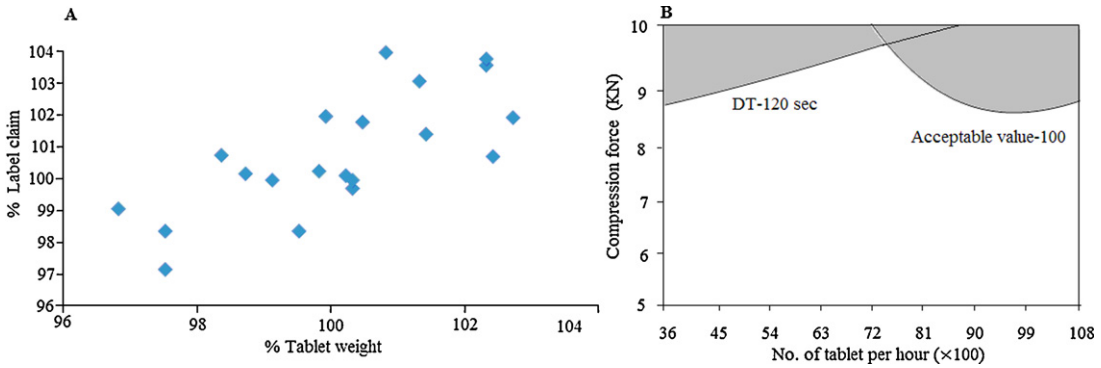

Fig. 10. (A) Correlation plot of tablet weight and drug content and (B) overlay plot showing relationship of DT and content uniformity to compression force and machine speed.

chances of demixing at higher blender speeds after 20 min of mixing. Blending time of 10 min was insufficient for achieving blend homogeneity at 6 rpm. This can be compensated by increasing the blending time to 15 min or increasing the blender speed to 12 rpm. In absence of the PAT tools the blending operation will be stopped at the target time shown in Fig. 8. Different combinations of blender speed, blend time and drug particle size can be selected from Fig. 8 to achieve blend homogeneity. The enhanced understanding of formulation and manufacturing variables provides regulatory flexibility post approval in varying these parameters within design space. This flexibility was restricted in traditional end product testing approach.

3.1.7. Study 7: effect of lubrication time on disintegration time

After lubricating the blend for 3 min, the DT of tablets (compressed at an average hardness of 50 N) was 42 and 56 s, respectively for formulations with 0.5% and 1.5% magnesium stearate (Fig. 9). The corresponding DT after 5 min of lubrication for these formulations was 55 and 70 s, respectively. Similarly the DT of tablets (compressed at an average hardness of 70 N) increased from 76 and 91 s at 3 min lubrication time to 90 and 104 s at 5 min lubrication time, respectively for formulations with 0.5% and 1.5% magnesium stearate. The DT of all the formulations was below the target value of 120 s which confirms that the blend was robust against effects of lubricant mixing time (at 12 rpm) up to 5 min. The blend was lubricated before compression to reduce the friction in die cavity during tablet formation and ejection of tablets from the die cavity. Magnesium stearate is a boundary lubricant which coats the granules (Hussain et al., 1990). The lubrication process was a time sensitive and beyond a certain degree of mixing, the disintegration time increased with reduction in hardness. Lubrication blend time optimization based on time and speed of blender was a good method to understand effects of over lubrication on hardness, DT and dissolution. Different on-line process analytical tools would be proposed to determine the optimum lubrication time, however near infrared spectroscopy was found not sufficiently sensitive as it could not predict the over lubrication (Hiyama, 2009).

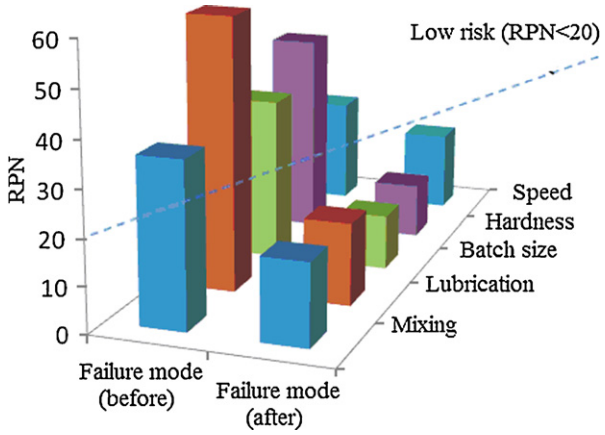

Fig. 11. FMEA analysis of manufacturing process.

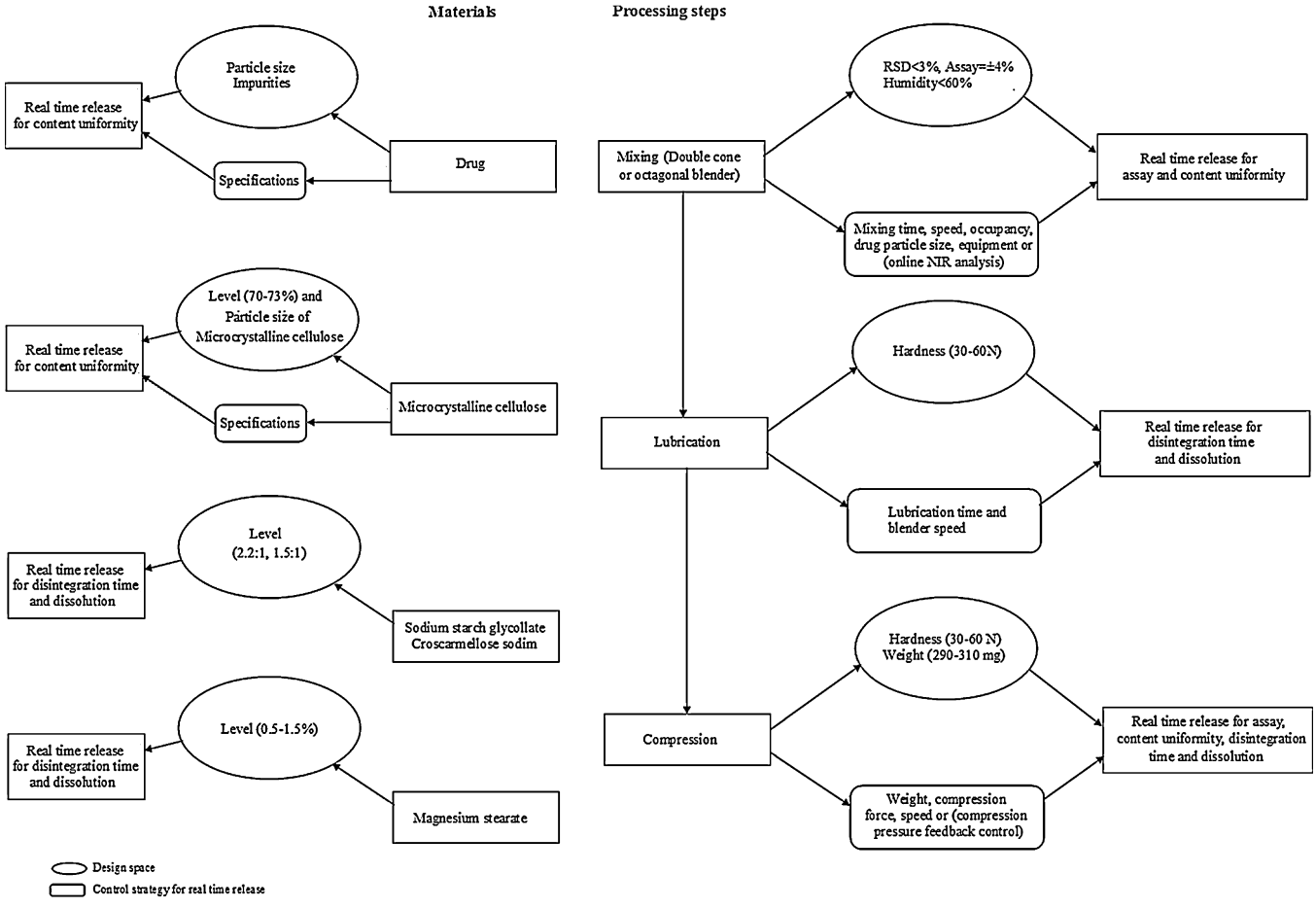

Fig. 12. Design space and control strategy for dispersible tablets.

Table 3
Risk assessment by PHA after developing product, process understanding and control strategy.

Quality attributes	Effect of API attribute on drug product quality							Effect of excipients on drug product quality				Effect of unit operations on drug product quality			
	Salt form	Particle size	Solubility	Stability	Purity	Residual solvent	Moisture	Microcrystalline cellulose	Croscarmellose sodium	Sodium starch glycollate	Magnesium stearate	Mixing	Lubrication	Compression	Packaging
Appearance	–	–	–	–	–	–	–	–	–	–	–	–	–	Fig. 10A and B	–
Identification	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Microbiology	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Disintegration time	–	–	–	–	–	–	–	– Fig. 4A	– Fig. 5A and B	– Fig. 5A and B	– Fig. 6	–	– Figs. 6 and 9 (CS)	Fig. 10B (CS)	–
Dissolution	–	– Fig. 4C	– Fig. 4C	–	–	–	–	–	– Fig. 5A and B	– Fig. 5A and B	– Fig. 6	–	– Figs. 6 and 9 (CS)	Fig. 10B (CS)	–
Hardness	–	–	–	–	–	–	–	–	–	–	– Figs. 6 and 9	–	– Fig. 9 (CS)	Fig. 10B (CS)	–
Assay	–	–	–	–	Specs (CS)	–	–	–	–	–	–	– Fig. 8 (CS)	–	–	–
Content uniformity	–	– Fig. 9 (CS)	–	–	–	–	–	– Spec (CS)	–	–	–	– Fig. 8 (CS)	–	– Fig. 10A and B (CS)	–
Flow	–	– Fig. 4B (CS)	–	–	–	–	– Spec (CS)	– Fig. 4B	–	–	–	–	–	–	–
Taste	– (Free acid)	–	– (Free acid)	–	–	–	–	–	–	–	–	–	–	–	–
Degradation	–	–	–	–	–	–	–	–	–	–	–	–	–	–	– Fig. 7
Impurities	–	–	–	– Specs (CS)	– Specs (CS)	– Spec (CS)	– Spec (CS)	–	–	–	–	–	–	–	–

(–) low, (+) medium; and (++) high. CS = control strategy, Specs-specification.

3.1.8. Study 8: effect of tablet compression process on CQAs

The data presented in Fig. 10A showed excellent content uniformity with RSD of less than 4% and correlated well with the tablet weight. Tablet friability was found less than 1% in all cases and hence was not considered further. At higher compression force, harder tablets were produced with longer disintegration time. As shown in Fig. 10B, below compression force of 7.59 kN, DT and acceptance value were less than target 2 min and 10, respectively. Controlling hardness within the selected range would ensure complete dissolution and content uniformity. A feed-back system in the form of online monitor could be employed for controlling the compression pressure/force of tablets in the compression process. A compression pressure/force control permitted the correction of filled powder blend in the die cavity and removal of tablets out of specified range. Mean tablet weight information measured periodically by automatic sampling was the fed-back parameter to the compression pressure control system and corrections in filled powder blend in the die cavity were performed accordingly (Hiyama, 2009).

3.2. Design space and control strategy

CQAs were identified by the risk assessment and their relationship to critical material attributes/unit operations was established by multivariate experimental design (Rathore et al., 2007). This relationship known as "design space" is the space within which the quality of the product can be built. The wider the design space, the more robust and flexible the process is to accommodate variations. Risk assessment, multivariate experimental design, literature and prior experience/knowledge contribute in defining the design space. For dispersible tablets, the control strategy was developed after the estimation of residual risk and an assessment for its acceptability. The ICH Q8 (Food and Drug Administration, 2009) defines design space as "the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change; however the movement out of the design space is considered a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to the regulatory assessment and approval". The concentration of disintegrants and compression pressure were found to be critical in their influence on DT and dissolution of tablets. Fig. 11 depicts the FMEA analysis before and after the implementation of control strategy. RPN for all the possible failure modes were below 20 and hence rendered them low risk. When operated within the established design space, the compliance to dissolution and DT would be assured. Similarly, the design spaces for content uniformity and assay were developed and these tests did not need be performed on the finished product. Lepore and Spavins (2008) provided the guidance in defining a design space and Boukouvala et al. (2010) listed the methodology for defining design space for new processes where limited information was available. In addition, the effect of inlet air humidity on fluidization behaviour and granule size was studied by Lipsanen et al. (2007) and an operating window for the fluidized bed granulation were defined. Huang et al. used a combination of design of experiments and multivariate techniques to establish design space for achieving desired CQA's (Huang et al., 2009).

Design space limits are the basis of validation acceptance criteria (Boukouvala et al., 2010). Process verification confirms that the process is able to deliver acceptable product when operated within design space. Fig. 3 summarizes the design space for dispersible tablets. The risk of failure increased with the proximity of operating range of process variables to the design space boundary however whether such risks were significant was determined by ability of the control strategy to detect and mitigate the risk. Thus, success of the overall product and process performance would depend on the execution of an operating plan, including an appropriate control strategy and appropriate process monitoring. ISPE PQLI proposed model for control strategy which links QTPP to the manufacturing controls needed to deliver the objectives (Davis et al., 2008). The control strategy for the dispersible tablets is shown in Fig. 12 and the revised risk assessment after implementation of control strategy is shown in Table 3. The CQA's derived from QTPP were linked to the critical material and process attributes in Fig. 12. Compliance to assay and content uniformity is assured by using drug particle size, amount of MCC and compression parameters such as weight, speed and force of compression within design space. Similarly compliance to DT/dissolution is assured by using disintegrant amount, magnesium stearate amount, lubrication time and compression parameters within design space. Upstream shift in quality controls and adherence to the design space provides an opportunity to release the batch in real time. Increased product/process knowledge, risk management and quality management systems along with the use of PAT tools for in-line and on-line measurements further strengthen the real time release argument (EMEA, 2010). Under this paradigm, the finished product testing confirms the quality and is not needed for batch release. This represents the major shift from QbT approach where compliance to finished product testing in approved specifications is pivotal to the release of batch. FDA'S PAT guidance document (Food and Drug Administration, 2004) defined the real time release (RTR) concept as the ability of process data (valid combination of material attributes and process controls) to ensure in-process and final product quality. Besides increased process control and quality assurance, RTR offers other advantages including low analytical cost, low material cost, low rejection, low reworking and high yield. As the application of PAT tools for testing impurities is still evolving, the RTR is currently used for stable drugs. If all CQA are monitored and assured by in-process testing then end product testing may not be needed. Product testing will continue to be used for stability studies. In the event of the breakdown of equipments/instruments, the control strategy should be provided in the application for using alternative tests like in-process and finished product testing. Failure of a product should be investigated and trending should be followed. Batch release in these cases will depend on the outcome of such investigations and should comply with GMP principles (EMEA, 2010).

4. Conclusion

Innovative approaches such as quality management programs, process capability measurements, six sigma, lean manufacturing and continuous improvement programs can be adopted to improve the quality of dispersible tablets. Understanding the relationship between critical material and critical process attributes culminates in process control and continuous improvement. Disintegrant amount and compression force were identified as the two major critical parameters for meeting goals set in QTPP. Dispersible tablets with desired DT could be prepared in the larger area of design space and various combinations of hardness and disintegrants could be selected. Similarly, combinations of blend time, blender speed and drug particle size were selected to achieve the blend homogeneity. Compression force of less than 7.59 kN produced tablets with acceptable DT and content uniformity. Operating within the design space provided the flexibility in releasing the batch in real time. Consequently, this study marked a possibility of a major shift from traditional QbT approach to enhance the manufacturers' confidence in their products as well as to relieve the FDA work load significantly as quality is built in the system.

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