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Formulation and Design of Multiunit Particulate System (MUPS) Tablet of Pantoprazole by QbD : Study Effect of Formulation Variables on Tablet Characteristics

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Abstract: In this present study an attempt was made to prepare multiunit particulate system (MUPS) tablet containing Pantoprazole (PTZ) by applying QbD principle. The critical formulation variables were identified and effects of these variables on Critical Quality Attributes (CQAs) were studied. A full factorial design was applied to optimize the formulation and to develop design space for Pantoprazole multiunit particulate tablets. The formulation variations those chosen for the study were; quantity of dry polymer (X_1), quantity of PlasACRYL HTP20 (X_2) and percentage of pellets in tablet (X_3). And the various responses, that to be observed or affecting were percent release of drug in 0.1N HCl (Y_1), percent release in phosphate buffer pH 6.8 (Y_2), hardness (Y_3), disintegration time (Y_4) and percent friability (Y_5). No design was framed for those formulations where X_1 was below 91.5 mg and X_3 was above 42 percent to prepare Pantoprazole multiunit particulate tablets. The operating ranges, for robust development of Pantoprazole multiunit particulate tablets of desired quality were decided as follows, X_1 between 91.5-115mg, X_2 between 23-34mg and X_3 between 25-42% respectively. Drug release profile of the final selected formulation V4 found comparable with reference product and value for similarity factor f2 was 56.5. Not only did the ternary mixture of X_1, X_2 and X_3 control the dissolution profile and physical characteristics of tablets, but also physical parameters contributing to achieve desired dissolution profiles. It could be concluded that a promising Pantoprazole multiunit particulate tablet was successfully designed using QbD approach.
Key words: MUPS, PlasACRYL HTP20, FMEA, Cause and effect diagram, Risk priority number.

Introduction

The last decade had seen a noteworthy transformation in pharmaceutical quality regulation from an empirical process to a more science and risk-based approach. There are two approaches for pharmaceutical development, the empirical and systematic (pharmaceutical quality by design, QbD) approaches. QbD is a systematic risk-based, proactive approach to pharmaceutical development that begins with pre-defined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management[1]. Thus, QbD is concerned with the achievement of certain predictable qualities with desired and predetermined specifications through relating the critical material attributes (CMAs) and critical process parameters (CPPs) to the critical quality attributes (CQAs) of drug product. It uses multivariate experiments to understand product and process and to establish a design space through design of experiments (DoE)[2]. In the QbD context, for a product to be of consistent quality the process must be very well understood.

Therefore, all its sources of variability (coming from the raw materials, the environment and the process itself) must be indentified and explained; afterwards, that at the end, consistent product quality is ensured[2,3,4].

Building from the QbD scheme, methods can be used upstream at the beginning stages of research, development and design phases, mean while the product quality should be proactively controlled in the manufacturing process. The application of QbD scheme in pharmaceutical development has three steps. In first stage, defined Quality Target Product Profile (QTPP), identify CQAs and the potential risk factors are determined by risk assessment in the initial design during product development. In second stage, carry out the development batches with multivariate to improve process knowledge using DoE wherever needed and reduce the risk based on the experiment results. In last stage, define design space, use quality management tools to manage the risk and finalize control strategy (CS).

To improve process knowledge, statistical DoE is valuable tool to establish in mathematical form the relationships between CMAs, CPPs and CQAs[2,3,4]. A range for each process parameter and their combinations can be defined, in which the desired CQAs values are achieved. Also, a range for the quality of combinations of raw material attributes and process parameters that need to be realized by the process, to ensure that the CQAs stay within the DS.

Pantoprazole is a substituted benzimidazole derivative that inhibits gastric acid secretion by irreversibly binding the proton pump (H+/K+-ATPase) in the gastric parietal cells[5]. It is used for the treatment of gastrointestinal conditions particularly peptic ulceration, Zollinger–Ellison syndrome and reflux esophagitis[6,7]. Pantoprazole is unstable at low pH values. The highest stability of this drug is achieved at a pH value higher than 5.5. Therefore, Pantoprazole is commercially formulated as enteric coated tablets or capsules[8].

In recent years, a continuous interest has been focused on the development of formulations using multiparticulate systems, offering various advantages over single dosage forms, namely, an improved bioavailability[9,10] easy administration for elderly people and for children[11]. These include a low risk of dose dumping, flexibility of blending units with different release patterns, reproducible gastric residence time, and prevention of high local drug concentration in the gastrointestinal tract[12,13], low intra- and inter-subject variability in plasma levels and bioavailability[14], reduction of irritation of the gastric mucosa due to drug degradation of simple units[9,15] and divided in to desired dose strengths without formulation changes[16].

Compression of coated particles like pellets to disintegrating tablets combines the advantages of oral, multiple-unit dosage forms[17,18] with those of tablets, i.e. cost effectiveness and divisibility. The orally disintegrating MUPS tablet medication can be taken without water, especially while travelling since the dosage form can be designed as orally disintegrating preparation that contains flavours and sweeteners that stimulate salivation and swallowing, e.g. Prevacid SoluTab[9] and suitable pediatric and geriatric patients.

In earlier work, lansoprazole fast-disintegrating tablet developed, by adjusting the ratio of methacrylic acid copolymer dispersion to ethyl acrylate–methyl methacrylate copolymer dispersion to 9:1 and adding a 20% triethyl citrate concentration in the enteric layer of microgranules to have sufficient stability against compression forces.[19,20].

In recent decade, pantoprazole sodium enteric-coated tablets developed were prepared by direct compression of the enteric-coated pellets and suitable excipients. The optimized formulation was: the coating level is 55%, the plasticizer content is 20%, the ratio of Eudragit L30D-55/NE30D is 8:2, enteric-coated pellets/ excipients is 5 : 5[21]. In recent works two polymers are mostly used, one is enteric coating polymer and another to improve flexibility of enteric coat of pellets used for compression in MUPS tablet formulation by the researcher.

In enteric coating formulation, along with polymer(s), plasticizer and glidant are also significantly contributing to enteric properties. It is critical to optimized all these formulation variables especially when more critical parameters also needs to optimize simultaneously. In this research, first time study of simultaneous effect of concentration of enteric polymer, glidant, plasticizer, pellets concentration using DoE. PlasACRYL HTP20, ready mix of glidant (GMS, Glyceryl monostearate) and plasticizer (TEC, Triethyl citrate), has been used in enteric coating. There has been abundant literature on use of GMS as a glidant in film coating. Problem of using GMS separately in film coating is its complexity to use, since GMS needs to be heated and cooled to

prepare an emulsion which is a time consuming procedure. Use of ready mix, PlasACRYL HTP20, has reduced preparation time of enteric coating dispersion and assurance of consistency.

The purpose of the study was to develop of pharmaceutical equivalent formulation with the brand product of PTZ MUPS tablet, target of the study was to have minimum tablet weight, sufficient oro-dispersible properties, chemically and physically stable formulation using single polymer and ready mix plasticizer by QbD principle. The QbD scheme implemented in three phase: 1) Risk assessment - initial risk assessment carried out using cause and effect diagram and FMEA tool for formulation variables, 2) Risk reduction - based on results of design of experiments batches and 3) Risk control - using DS, FMEA tool and CS.

Material and Method

Materials

Pantoprazole sodium sesquihydrate was gifted from Hetero drugs. Povidone (Kollidon 30, BASF, Germany), Sodium Carbonate anhydrous (Sujata Chemicals, India), Polysorbate 80 (Kolliphor PS 80, BASF, Germany), Talc (Standard grade, IMERYS, France), Low-Substituted Hydroxypropyl Cellulose (L-HPC LH-31, ShinEtsu, Japan), Microcrystalline cellulose (Celpheres® CP-203, Ceolus® KG 1000, Asahi Kasei, Japan), Hypromellose (HPMC VLV, HPMC 6cps, Dow Chemical, USA), Methacrylic Acid Copolymer Dispersion (Eudragit® L30D-55, Evonik, Germany), PlasACRYL® HTP20 (Emerson, USA), Polyethylene Glycol (PEG 6000, Clariant Produkte, Deutschland), Neotame (The Nutrasweet Company, Augusta), Red Oxide of Iron (Roha Dyechem, India), Microcrystalline cellulose (Avicel® PH 200, FMC Biopolymer, Germany), Mannitol (Pearlitol® 400 DC, Pearlitol® Flash, Roquette, France), Crospovidone (Kollidon CL-SF, BASF, Germany), Strawberry flavour (International Flavours and Fragrances, USA), Colloidal silicon dioxide (Aerosil® 200 Pharma, Germany), Magnesium stearate (Nitika, India) were used in trials.

Methods

Formulation design

The design of PTZ MUPS tablet formulation is provided in , Figure 1, MCC sphere (Celphere CP-203) used as starter core.

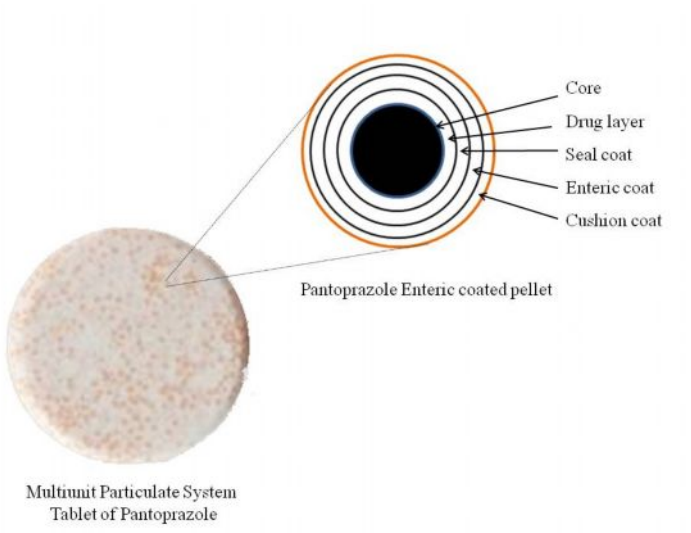


Figure 1. Formulation design for multiunit particulate system tablet of Pantoprazole

Preparation of drug layered pellets

Pantoprazole, povidone, sodium carbonate anhydrous and polysorbate 80 were dissolved in purified water followed by addition of aqueous homogenized (Ultra-turrex®, IKA, Germany) dispersion of talc and mixed for 30 min using mechanical stirrer (Remi Elektrotechnik Ltd, India). Dispersion was then strained

through 80 mesh screen. 500gm of CP-203 pellets were loaded in Wurster (GPCG 1.1, Glatt) and coated using 1.0 mm spray nozzle with a spray rate of 4-11 g/min, 0.9-1.1 g/min of atomization air pressure, 45-60 cfm of air volume and temperature 35-38 °C.

Table 1. PTZ MUPS formulation

Ingredients	mg/tab
I. Drug Loading	
Pantoprazole Sodium Sesquihydrate	45.1
Povidone (PVP K30)	7.5
Sodium Carbonate, anhydrous	10.0
Polysorbate 80	0.4
Purified Talc	4.5
LHPC LH-31	7.5
Celpheres CP-203	30.0
Purified Water	q.s
II. Seal Coating	
HPMC VLV	10.5
Purified Talc	3.2
Purified Water	q.s
III. Enteric Coating	
Eudragit L30D-55	80-120
HTP 20	22-34
Purified water	q.s
IV. Cushion Coating	
PEG 6000	8.0
HPMC 6cps	0.8
Neotame	1.0
Purified Talc	1.0
Red Oxide of Iron	0.1
Purified Water	q.s
V. Blending and Lubrication	
Ceolus KG-1000[§]	5%
Pearlitol Flash[¥]	q.s
Avicel PH 200[¥]	q.s
Pearlitol DC 400[¥]	q.s
Crospovidone*	8%
Neotame*	0.5%
Strawberry flavour*	1.0%
Aerosil 200*	0.5%
Magnesium stearate*	0.5%

Preparation of seal coated pellets

Hypromellose was dissolved in purified water followed by addition of aqueous homogenized (Ultra-turrex®, IKA, Germany) dispersion of talc and stirred for 30 min using mechanical stirrer (Remi Elektrotechnik Ltd, India). Dispersion was then strained through 80 mesh screen. 500 gm of drug pellets were loaded in Wurster (GPCG 1.1, Glatt) and coated using 1.0 mm of spray nozzle with a spray rate of 4-10 g/min, 0.9-1.1 g/min of atomization air pressure, 45-60 cfm of air volume and temperature 38-42 °C.

Preparation of enteric coated pellets

Prior to use PlasACRYL HTP20 was shaken well in container. Then this PlasACRYL HTP20 was added in Eudragit L30D-55 dispersion under slow stirring followed by addition of purified water. The dispersion was stirred for 30 min using mechanical stirrer (Remi Elektrotechnik Ltd, India) and strained through 100 mesh screen. 500 gm of seal coated pellets were loaded in Wurster (GPCG 1.1, Glatt) and then coated using

1.0 mm of spray nozzle with a spray rate of 4 -7 g/min, 0.9-1.2 g/min of atomization air pressure, and 45-60 cfm of air volume and temperature 28-30 °C.

Preparation of cushion coated pellets

Hypromellose, PEG 6000 and neotame were dissolved in purified water, followed by addition of aqueous homogenized (Ultra-turrex®, IKA, Germany) dispersion of talc and colour, mixed for 30 min using mechanical stirrer (Remi Elektrotechnik Ltd, India). Dispersion was then strained through 80 mesh screen. 500 gm of enteric coated pellets were loaded in Wurster (GPCG 1.1, Glatt) and coated using 1.0 mm of spray nozzle, spray rate of 4-10 g/min, 0.9-1.1 g/min of atomization air pressure, 45-60 cfm of air volume and temperature at 38-42 °C.

Blending

Weighed quantity of pellets and extra-granular excipients (mentioned in Table 1) and lubricated blend were taken as per Table 2. All extragranular excipients were sifted through 40 mesh sieves. Cushion coated pellets co-sifted with Ceolus through 30 mesh sieves, labeled as co-sift I. Crospovidone, flavour and neotame were co-sifted through 40 mesh sieves, labeled as co-sift II. Aerosil was co-sift with 1/4th quantity of Pearlitol 400 DC through 40 mesh sieves, labeled as co-sift III. Pre-sifted Avicel PH 200 was mixed with co-sift I followed by co-sift II, co-sift III, pre-sifted Pearlitol flash and remaining Pearlitol 400 DC in double cone blender and rotated for 300 revolutions and then finally added the sifted magnesium stearate and rotated for another 50 revolutions.

Tabletting

Tablets were compressed using P2020 tablet press (Fette, Germany) applying compression force of 8.0 - 17.0 kN, 2.0-4.5 kN of pre-compression force, 25-30 rpm of turret speed and 20-45 rpm of feed frame speed. Suitable flat faced beveled edge punch tooling dimensions selected as per tablet weight. The prepared tablets were stored in tightly packed double poly bag to protect from environmental exposure.

In-process parameters

During compression, the tablets were checked for tablet in process quality control parameters like hardness, thickness, friability, disintegration time, weight variation.

Assay

Assay of tablet was performed as per Pantoprazole Sodium Delayed-Release Tablets USP monograph (USP37-NF32)[22].

Dissolution studies

Dissolution studies were carried out in two stages. Dissolution in acidic condition i.e., simulated stomach condition was performed in USP apparatus II, dissolution medium used was 1000 ml of 0.1 N hydrochloric acid at a speed 75 rpm and temperature 37±0.5 ^{o}C for 120 min followed by dissolution in simulated intestinal condition using USP apparatus II, dissolution medium used was 1000 ml of phosphate buffer pH 6.8 at a speed 75 rpm and temperature 37±0.5 ^{o}C for 30 min.

Hardness

Tablet hardness was measured from the force required to fracture tablets by diametrical compression using a tablet hardness Tester (Erweka TBH200, Germany). Mean hardness of 5 tablets from each formulation was observed and reported as tablet hardness.

Disintegration time

Disintegration time is the time required for tablet to disintegrate completely without leaving any solid residue on mesh. *In vitro* disintegration time for oro-dispersible tablet (ODT) was measured using USP General Chapter[23]. A disintegration tester (EF-2W, Electrolab, India) was used in this study as a disintegration apparatus and distilled water (800 ml) as disintegration medium.

Friability

Friability of tablets was determined using Friabilator (Electrolab, India). Ten tablets were subjected to the combined effect of abrasions and shock in a friabilator at 25 rpm and dropping. The percent friability was then calculated by,

Percent Friability = (W-Wo/W) x 100

Where, Wo is the weight of the tablets before the test and W is the weight of the tablet after the test.

Preliminary trials

On the basis of prior knowledge and experience the initial risk assessment was performed. Risk factors involved from core to lubricated blend stage presented in cause and effect diagram (Figure 2). The preliminary trials were planned to reduced risk with formulation factors. MCC pellets were selected as core pellets as it has several advantages over sugar spheres. Quantity and size of core pellets were optimized and finalized to 30 mg/tab and 150 to 300 µm respectively. Seal coating was optimized to have efficient barrier coat and to reduce process time. Newly introduced HPMC VLV polymer used up to 20% of solid concentration and found that the film forming capacity was equivalent to regularly used low viscosity hypromellose grades. The 10.5 mg of HPMC VLV and 3.2 mg of talc per tablet were optimized for seal coating. Eudragit L30D-55 and PlasACRYL HTP20 were varied from 70 to 120 mg and 20 to 38 mg respectively. However, it was observed that at higher level of both the ingredients may cause severe process issues. Compressions were performed with various ratios of Eudragit L30D-55 and PlasACRYL HTP20 coated pellets with pre-optimized extragranular excipients but it was found that drug release was more than 10% in acidic media. Keeping this observation in mind the enteric coated pellets were further coated with cushion coat using PEG 6000 as cushioning agent and these pellets when compressed to tablet, they have reduced % of drug release compared to tablet with no cushion coated pellets. It was also observed as concentration of PEG 6000 increased in the formulation the drug released in acidic media decreased, however pellets were fussed, which increased the disintegration time more than 5 min. Hence PEG quantity optimized to 8.0 mg in cushion coat. Extragranular excipients and their quantity were finalized at initial stage using initial trials with pellets. The polymer level, plasticizer level and pellets level in tablet were considered as high risk formulation variable for further studies showed in Figure 2.

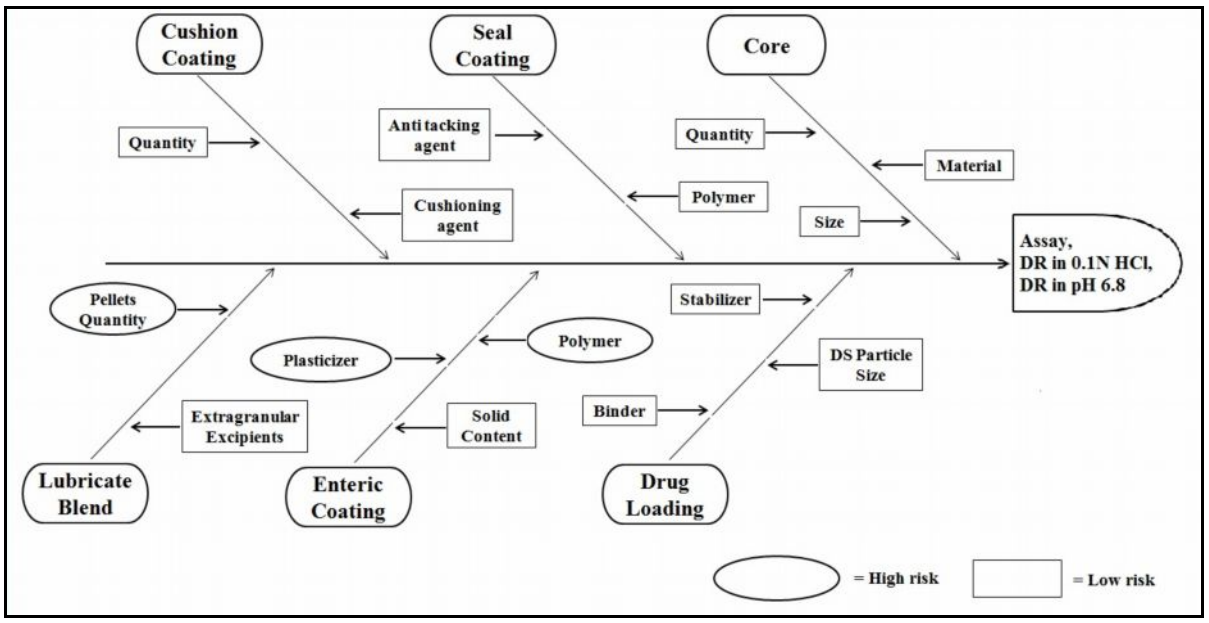


Figure 2. Initial risk assessment of the formulation variables

Experimental design

A 2^3 full factorial design was applied to explore the quadratic response surfaces and for constructing a second-order polynomial models using Design Expert (Version 8.1.6; Stat-Ease Inc., Minneapolis,

Minnesota). A design matrix comprising 10 experimental runs including 2 center point experiments was constructed.

The independent variables selected were the quantity of dry polymer (X_1), quantity of PlasACRYL HTP20 (X_2) and percentage of pellets in tablet (X_3). The dependent variables were release of drug in 0.1N HCl at 120 min (Y_1), release of drug in phosphate buffer pH 6.8 at 30 min (Y_2), hardness (Y_3), disintegration time (Y_4) and friability (Y_5). The concentration range of independent variables presented in Table 2 along with their low, medium, and high levels, which were selected based on the results from preliminary trials and observed responses.

Table 2. 2^3 full factorial design matrix, successful operating range and results

Trial	Independent (Formulation) variables*			Responses (CQAs)*				
	X_1 (mg)	X_2 (mg)	X_3 (mg)	Y_1 (%)	Y_2 (%)	Y_3 (N)	Y_4 (Sec)	Y_5 (%)
F1	-1 (80)	-1 (22)	-1 (25)	12	78	43	15	0.45
F2	1 (120)	-1 (22)	-1 (25)	8	85	41	14	0.64
F3	-1 (80)	1 (34)	-1 (25)	7	72	55	24	0.26
F4	1 (120)	1 (34)	-1 (25)	2	81	52	23	0.27
F5	-1 (80)	-1 (22)	1 (50)	18	81	32	6	0.75
F6	1 (120)	-1 (22)	1 (50)	17	88	34	9	0.79
F7	-1 (80)	1 (34)	1 (50)	11	75	38	12	0.62
F8	1 (120)	1 (34)	1 (50)	13	83	43	11	0.68
F9	0 (100)	0 (28)	0 (37.5)	3	79	45	8	0.42
F10	0 (100)	0 (28)	0 (37.5)	2	80	43	7	0.55
Successful operating range →				<10	$70 < Y_2 < 80$	>30	<30	<1.0

*X_1 : Quantity of Dry Polymer, X_2 :Quantity of PlasACRYL HTP20, X_3 : Percentage of Pellets in tablet, Y_1 : Release in 0.1N HCl (at 120 min), Y_2 : Release in pH 6.8 (at 30 min), Y_3 : Hardness, Y_4 : Disintegration time, Y_5 : Friability

Risk assessment

Cause and effect diagram was constructed to identify the potential risks with formulation variables and corresponding causes. Study covered formulation variables and study related to process variables (i.e. coating and compression process) covered in next articles. Drug release in 0.1N HCl at 120 min and drug release in pH 6.8 at 30 min were selective CQAs where as hardness, disintegration time and friability were in process CQAs. Based on previous knowledge and initial experimental data, failure mode and effect analysis (FMEA) method were further applied in the risk analysis of the parameters of the formulation variables.

In the traditional FMEA, the risk priority number (RPN) is used to conduct the risk assessment. The Potential failure shows the risk factors as Severity (S), Occurrence (O) and Detection (D). The three factors are all scored from 1 (best) to 10 (worst) on the basis of degree[24,25]. RPN is the product of occurrence, detection, and severity, which is expressed as, RPN = S x O x D, where O is the occurrence probability or the likelihood of an event occurring; we ranked these as 8-10, likely to occur; 4-7, 50:50 chance of occurring; and 1, unlikely to occur. The next parameter S, the severity, which is a measure of how severe of an effect a given failure mode would cause; we ranked these as 8-10, severe effect; 4-7, moderate effect; and 1, no effect. The final parameter D is the detectability or the ease that a failure mode can be detected, because the more detectible a failure mode is, the less risk it presents to product quality. For D, we ranked 1-3 as easily detectable, 4-7 as moderately detectable, and 8-10 as hard to detect.

The RPN threshold was set at 80, and any formulation variable with an RPN 40 or above was regarded as a potential critical factor, that is, potential risks are evaluated by subsequent formulation variable studies since it possibly has a potential impact on CQAs and in consequence on product safety and efficacy, while factors with a lower RPN can be eliminated from further study[26,27].

Identification of CQAs

The purpose of this work was to develop orally disintegrating MUPS tablet of PTZ. Before start the designed trials, CQAs were indentified. As by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product[2]. In this work, challenge was to maintain drug release less than 10% in acidic media, to match the dissolution profile with brand product in buffer media as dosage design has tendency of alteration of drug release characteristics after compaction into tablets[8].

Weight variation and content uniformity are another challenge due to size and density variation of lubricated blend components; however risk is reduced by selecting proper extra-granular excipients and blending parameters to overcome this issue. In orally disintegrating PTZ MUPS tablets, the coated pellets were compress to tablet with sufficient hardness and reduced disintegration time and low friability without damaging the film coatings. It is also important that care should be taken to protect chemical characteristics and physical properties of MUPS tablet. The drug product CQAs are the drug release in acidic media and buffer media where as in process CQAs are the tablet hardness, disintegration time and friability, which are to be fixed.

Development of design space of PTZ MUPS tablets having optimum quality

The relationship between the formulation variables and CQAs were described in the DS. DS was determined from the common region of successful operating ranges for multiple CQAs discussed in Table 2. It is expected that operation within the DS will result in a product possessing the desired CQAs.

Determination of control strategy of the optimized PTZ MUPS tablets

A control strategy is designed to ensure that a product of required quality will be produced consistently[2]. The acceptable range of material attributes were determined based on DS.

Results and Discussion

Risk assessment

Initially, risk assessment aims to obtain all the potential high impact factors which will be subjected to a DoE study to establish a product DS. It has been outlined in the ICH Q9 document, risk identification and risk analysis are two basic components of risk assessment. The first step in the risk assessment was to systematically gather up all the possible factors that could influence product quality. Various factors that affect were organized hierarchically to control the risk factor based on literature data, previous study experiences[28], pre-formulation data and cause and effect diagrams[29].To initiate the FMEA, we divided the failure modes firstly into manufacturing steps those coming from the formulation and secondly the process, people, environment, and equipment based on preliminary experiments and/or prior knowledge. The variables that responsible for *in vivo* performance marked high scored. Results obtained can be used to identify high vulnerability elements and to guide resource deployment for best benefit. FMEA can be done at any time in the system from initial design to lifetime[30].

The RPN must be calculated for each cause of failure. RPN shows the relative likelihood of a failure mode, in that the higher number, the higher the failure mode. From RPN, a critical summary can be drawn up to highlight the areas where action is mostly needed[31]. RPNs were calculated as the product of frequency, severity and detectability scores. Failure mode scores could range from 1 to 1000[32]. We ranked S, O and P of 1-3 as best-case value, 4-7 as moderate-case value and 8-10 as worst-case value, and then a maximum RPN of 1000 and a minimum RPN of 1 are possible.

Preliminary trials

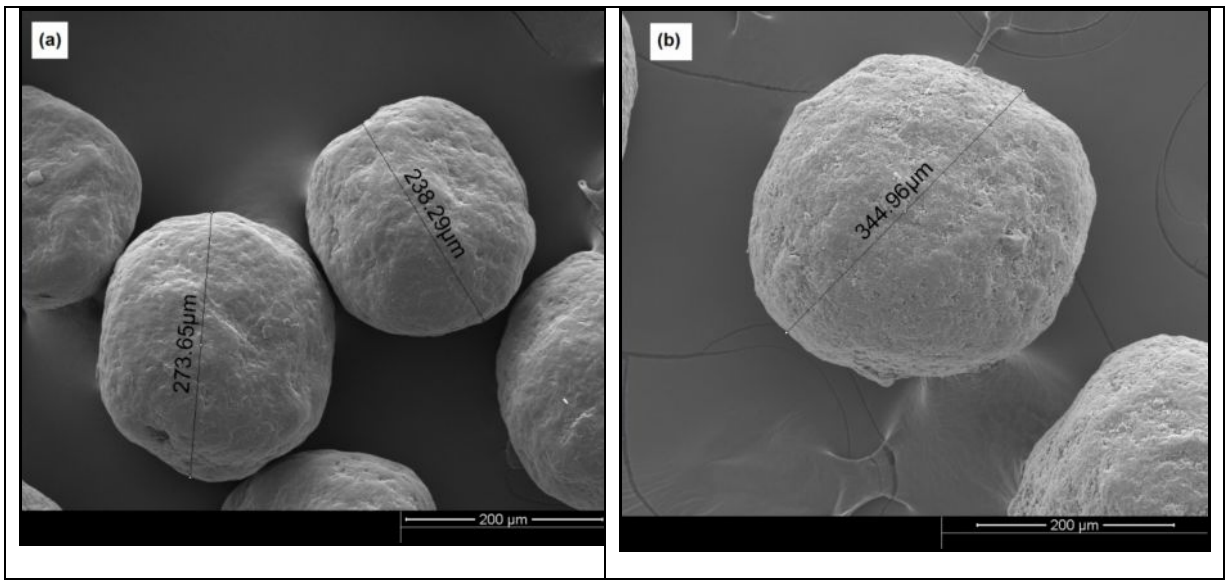
Anti-tacking agents and plasticizers are the important components when used along with Eudragit L30D-55 in enteric coating suspensions for efficient and effective coating . Talc, one of the commonly used anti-tacking agents, often poses processing issues such as sedimentation or nozzle clogging. GMS, a hydrophobic anti-tacking agent, can also provide increased film flexibility. In the process of emulsification of the TEC, GMS with polysorbate 80 is therefore needed to be incorporated into the aqueous coating formulation,

to overcome these problems. PlasACRYL HTP20, a newly designed coating additive, includes TEC, GMS and polysorbate 80 in concentrations in accordance with the standard recommendations for Eudragit L30D-55 coating formulations. This easy-to-use coating additive also contains the required amount of TEC as plasticizer[33,34].

Total three types of microcrystalline cellulose (MCC) used for the development of MUPS. Celpheres CP-203 prepared from MCC granulation used as starter core, which are strong, not brittle, and have a low elastic resilience than sugar spheres which beneficial for MUPS formulation. Avicel PH 200 has mean particle size of 180 µm and bulk density 0.35 g/ml[35]. Due to larger particle size, enhances flow also maintains the high levels of compressibility with minimum weight variation and content uniformity in pellets compression. Ceolus KG-1000 having the lowest bulk density i.e. 0.12 g/cm^3 among MCC grades[36]. Ceolus KG-1000 puts impact on blend flow at higher percentage in formulation. It has superior compatibility compared with PH-101 and other standard MCC grades. Ceolus KG-1000 particles have extremely large L/D value. The particles easily arrange perpendicularly to the applied force upon compaction; therefore the contact area of the MCC particles is increased. Entanglement of particles also easily occurred under compression force which provides additional compactibility[37-39].

In preliminary trials, each coating layer optimized and found quantity of Eudragit L30D-55, PlasACRYL HTP20, PEG 6000 and percentage of pellets had significant impact on tablets parameters physical as well as chemical. Level of Eudragit L30D-55 controls the drug release in acidic media while PlasACRYL HTP20 increased the flexibility of film which avoid the cracking of film due to compression force. However, in the preliminary studies it was found drug release was still more than specification. So an additional cushioning coat to enteric coated pellets was given to absorb the shocks due to compression and reduce drug release in acidic media. The PEG 6000 has tendency to fuss with the pellets at higher concentration. Hence the quantity of PEG 6000 was optimized and finalized for DoE trials. Percentage of pellets in tablet varied from 25 to 50% and found even with pellets coated with cushion coat. It was found if the percentage of pellets increased, the drug release in acidic media also increases. The SEM images of pellets at each stage presented in Figure 3.

It was concluded that quantity of polymer, PlasACRYL HTP20 and percentage of pellets in tablet had combined effect on drug release in acid media and physical parameters, hence these formulation factors finalized for DoE studies to investigate the main, interactive and quadratic effects.



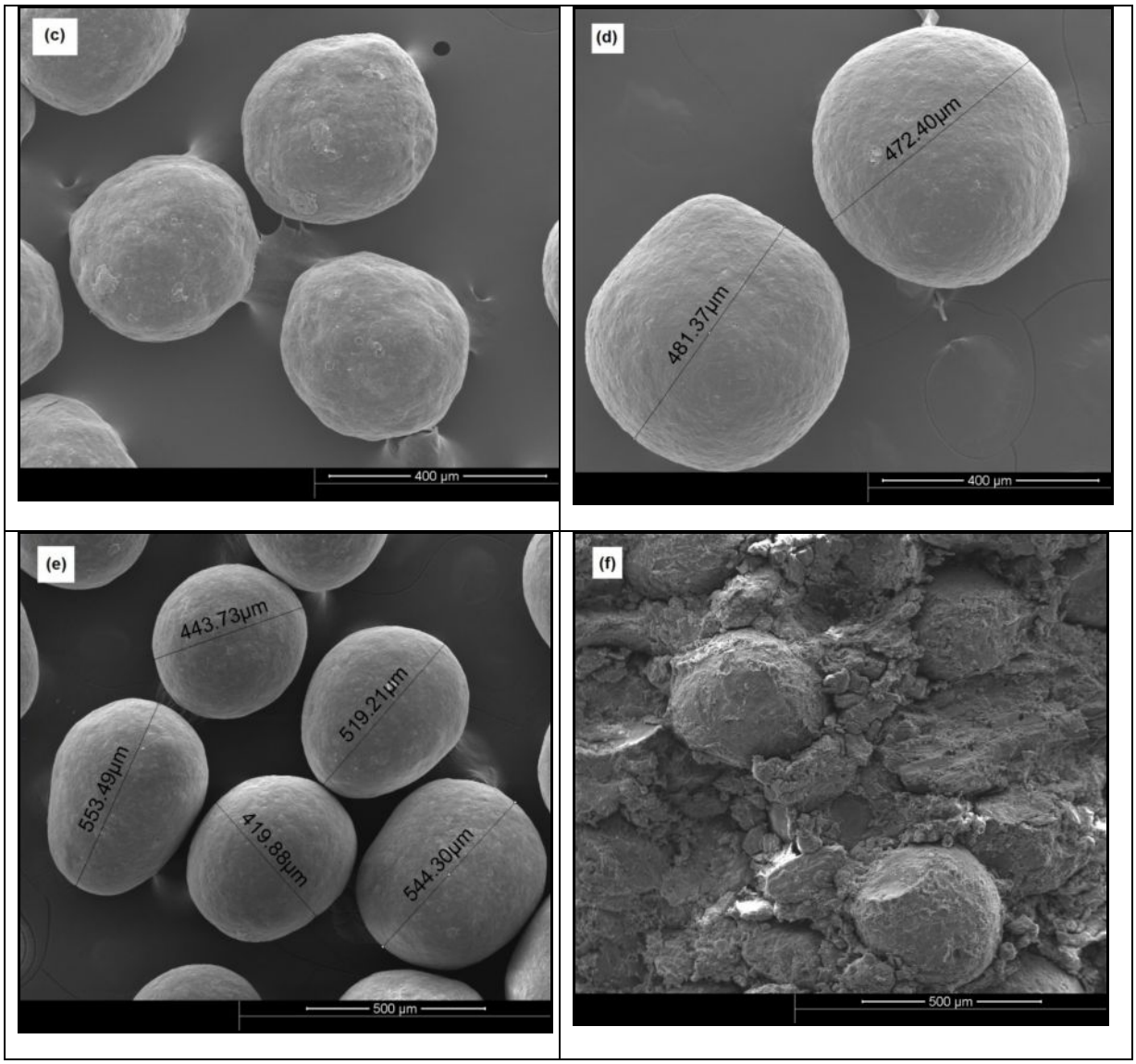


Figure 3. SEM images of a) Celphere CP-203 b) Drug loaded pellets c) Seal coated pellets d) Enteric coated pellets e) Cushion coated pellets and f) Cross section of tablet

Design of experiment

The aim of this work was to optimize the formulation variables to be incorporated with enteric coated pellets of PTZ into ODT MUPS. For ideal formulation, pellets should be kept at non ruptured after compression and should also exhibit adequate mechanical strength for the tablet to have low friability but should disintegrate quickly upon hydration.

Ranges of independent variables had been selected from the preliminary trials results. Eudragit L30D-55 was used as an enteric coating film former for solid-dosage forms. The coating was resistant to gastric juice but dissolves readily at above pH 5.5[35]. Since, Our preliminary trials result suggested that minimum 80 mg/tablet of Eudragit L 30 D-55 was required for acid resistant and beyond 34 mg/tablet of PlasACRYL HTP20, if used, were found to form agglomerated in some trials. As percentage of pellets reduced in tablet, the tablet weight increased which was not acceptable considering ODT design. The target was to keep low tablet weight and it should easily disperse on tongue, which is convenient for patient.

The results (Table 2) showed that the drug release in acidic media varied from 2 to 18%, the drug release in buffer media from 72 to 88%, hardness from 32 to 55N, disintegration time from 3 to 24 sec and friability from 0.26 to 0.79%. The wide variation in the drug release in acid media, disintegration time and friability values for different formulations and the high degree of reproducibility (Table 2) suggested that these responses are strongly dependent on the selected independent factors. Regarding drug release in buffer and

hardness, although small variations were noticed between different formulations, the results seemed to be systematic and repeatable, which may suggest dependency on the studied factors.

Analysis of variance (ANOVA)

ANOVA was performed to evaluate the significance of the quadratic models (linear, interactive and polynomial) on the responses and to estimate their quantitative effects. Table 3 summarizes the effects of the model terms and associated *p* values for all five responses. At a 95% confidence level, a model was considered significant if the *p* value < 0.05. The sign and value of the quantitative effect indicate trend and magnitude of the term's influence on the response, respectively. Positive signs indicate an increase in the response value, while negative signs demonstrate a decrease in the response value.

Table 3. Summary of results for testing validity of the models. DF indicates: degrees of freedom; SS: sum of squares; MS: mean of square; F: Fischer's ratio; p: probability; R^2: regression coefficient

	DF	SS	MS (Variance)	F	*P*	R^2
DR in Acidic media						
Model	4	193.50	48.38	64.50	0.0007	0.820
Lack of Fit	3	2.50	0.83	1.67		
DR in Buffer media						
Model	3	190.38	63.46	158.65	<0.0001	0.983
Lack of Fit	4	1.50	0.38	0.75		
Hardness						
Model	2	422.50	211.25	40.89	0.0003	0.922
Lack of Fit	5	29.00	5.50	2.90		
Disintegration Time						
Model	3	277.50	92.50	71.15	0.0002	0.778
Lack of Fit	4	6.00	1.50	3.00		
Friability						
Model	2	0.27	0.13	19.03	0.025	0.841
Lack of Fit	5	0.034	0.00845	0.79		

The results indicated that the drug release in 0.1N HCl (Y_1) of the tablets was significantly influenced by the linear models of quantity of dry polymer (X_1), quantity of PlasACRYL HTP20 (X_2) and percentage of pellets in tablet (X_3), in addition to the interactive model of quantity of PlasACRYL HTP20 - percentage of pellets in tablet (X_2X_3). Figure 4a portray the three-dimensional surface plot indicated that when X_2 increased from -1 level to +1 level, Y_1 was found to decrease linearly due to increase film flexibility and strength of the enteric coat help to protect drug in acidic media while when X_3 increased from -1 level to +1 level, Y_1 was found to increased linearly due to increased in cleavage of number of pellets result in increased drug release in acidic media. This study indicated that in MUPS tablets, level of plasticizer and percentage of pellets in the table governed the drug release in acidic media which had responsible to control the cleavage of pellets during compression compared to level of enteric coating polymer.

Drug release in pH 6.8 phosphate buffer (Y_2) was significantly influenced by the linear models of quantity of dry polymer (X_1), quantity of PlasACRYL HTP20 (X_2) and percentage of pellets in tablet (X_3). Three-dimensional surface plot (Figure 4b) indicated that when X_1 increased from -1 level to +1 level, Y_2 was found to increased linearly due to reduced degradation of active in acidic media and remaining active quantity release in buffer media while when X_2 increased from -1 level to +1 level, Y_1 was found to decreased linearly due to increased film flexibility and strength of the enteric coat.

Hardness (Y_3) and Disintegration time (Y_4) were significantly influenced by the linear models of quantity of PlasACRYL HTP20 (X_2) and percentage of pellets in tablet (X_3). Figure 4c-d portray the three-dimensional surface plot indicated that when X_2 increased from -1 level to +1 level, Y_3 and Y_4 were found to increased linearly could be due to pellets fussing increased during compression as concentration of PlasACRYL HTP20 (contains GMS and TEC) increased while when X_3 increased from -1 level to +1 level, Y_3 and Y_4 were

found to decreased linearly due to large content of pellets in the blend results in less compaction which make porous tablet.

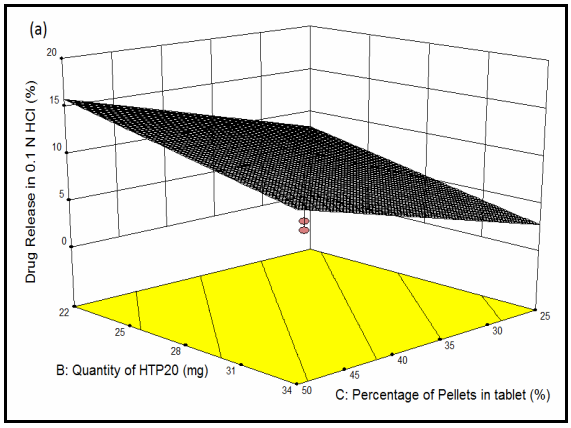
Friability (Y_5) was significantly influenced by the linear models of quantity of PlasACRYL HTP20 (X_2) and percentage of pellets in tablet (X_3). Three-dimensional surface plot (Figure 4e) indicated that when X_2 increased from -1 level to +1 level, Y_2 was found to increased linearly could be due to fussed pellets strengthen the tablet while when X_2 increased from -1 level to +1 level, Y_1 was found to decreased linearly due to increased porosity of the tablet reduced strength of the tablet.

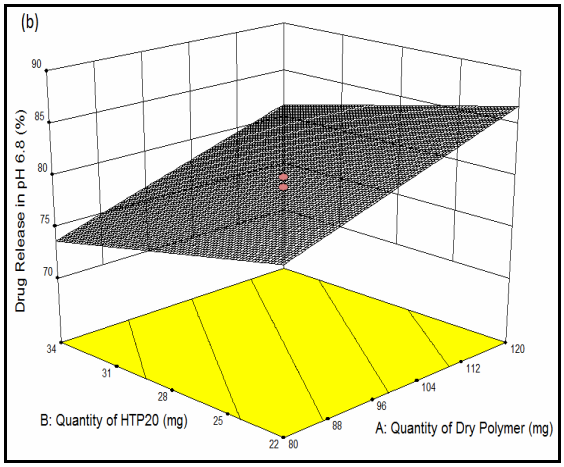
The resulting equation for all five responses are presented below:

$$Y_1 = 9.30 - X_1 - 2.75X_2 + 3.75\ X_3 + 1.25\ X_2\ X_3 \quad (1)$$
$$Y_2 = 80.2 + 3.87X_1 - 2.67X_2 + 1.37\ X_3 \quad (2)$$
$$Y_3 = 42.25 + 4.75X_2 - 5.50X_3 \quad (3)$$
$$Y_4 = 12.9 + 3.25\ X_2 - 4.75\ X_3 - 1.25X_1X_3 \quad (4)$$
$$Y_5 = 0.54 - 0.10X_2 + 0.15X_3 \quad (5)$$

Validity of model tested for statistical analysis. *p* values for all the simulated responses were well below the significant level (<0.05), suggesting that all the models were significantly in predicting their response values.

The correlation coefficients (R^2) for all five responses indicated good fits to the raw data (observed) in the revised model. However, lower correlation coefficients were obtained for drug release in acidic media (0.820), disintegration time (0.778) and friability (0.841). This might be explained as the influence of the fusion of pellets after compression change internal structure of different formulation is expected to show some variations. Moreover, the qualitative nature of the disintegration test that depends in accurately in evaluating the disintegration time can result in big error.





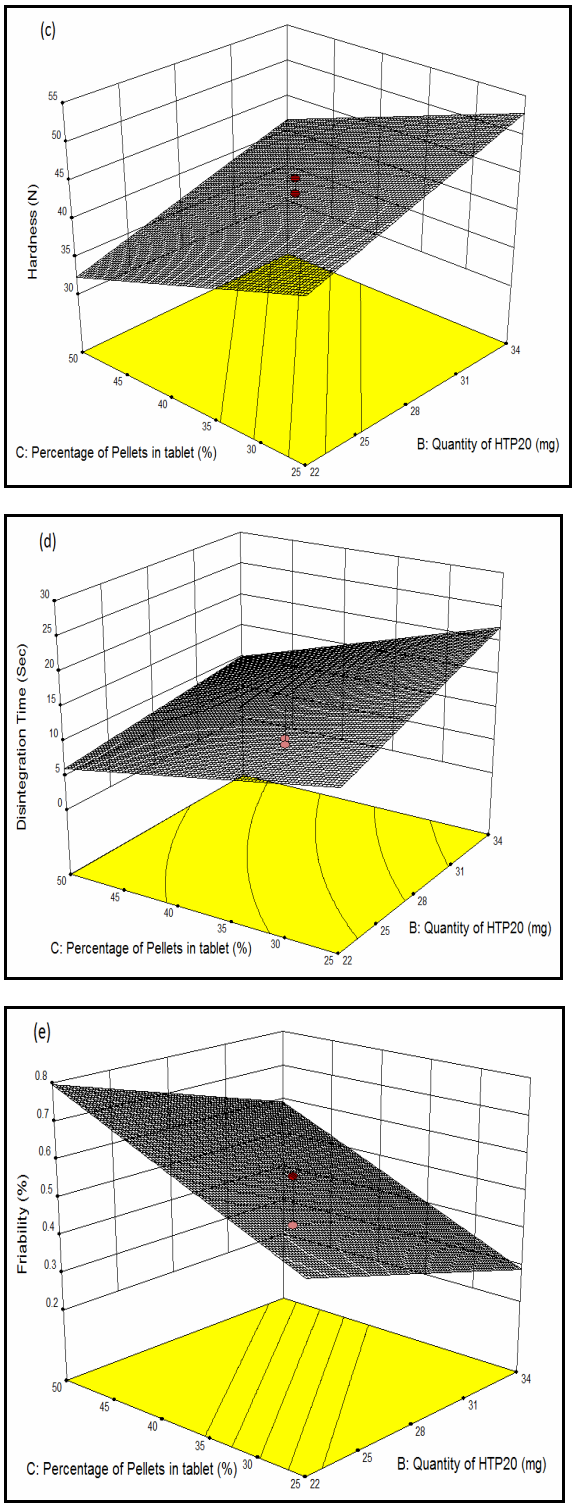


Figure 4. Response surface plot showing the influence of independent variables on - a) drug release in 0.1N HCl, b) drug release in pH 6.8 Phosphate buffer, c) Hardness, d) Disintegration time and e) Friability.

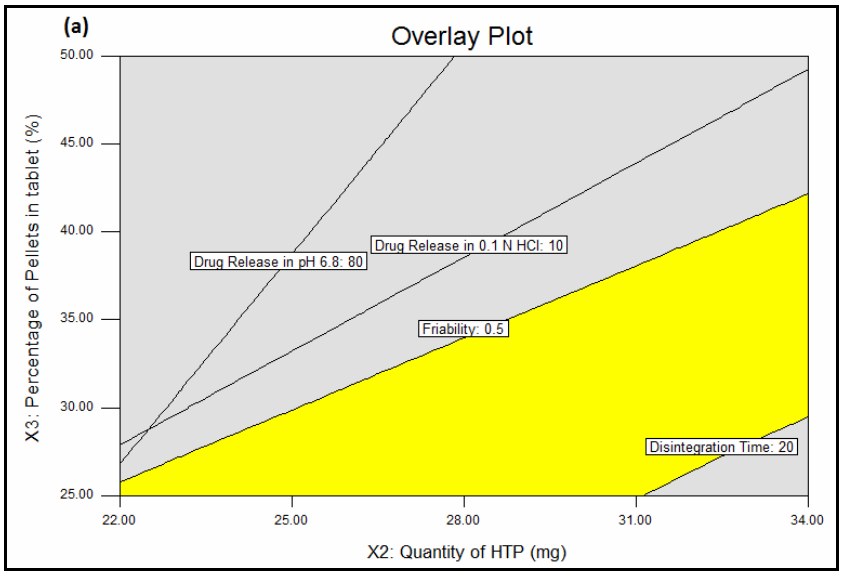
Experimental validation of design space

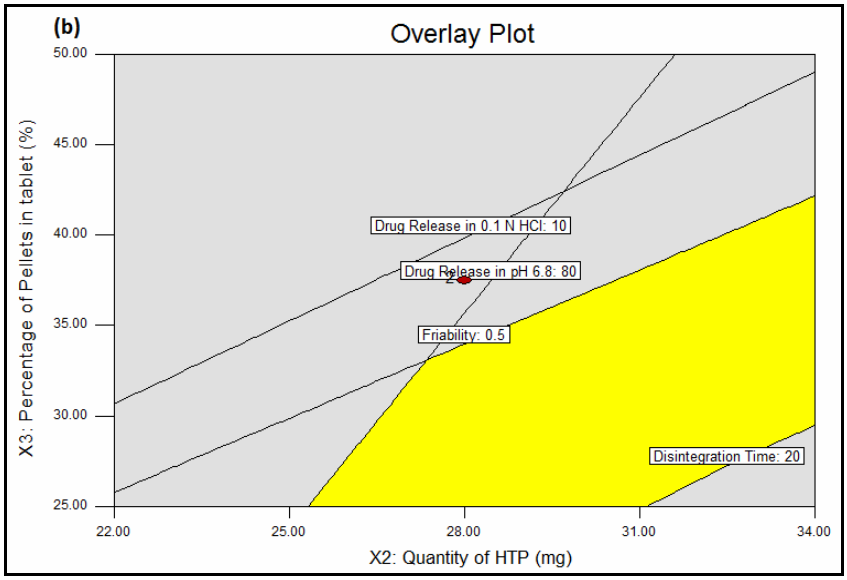
The multidimensional combination and interaction of independent variables and process parameters, that have been demonstrated to provide assurance of quality, is termed as the design space[2]. DS could be determined from the common region of successful operating ranges for the two responses. Experimental validation of DoE trials was undertaken by fabrication of optimized process variables. For optimized formulation variables, levels of factors which provided drug release in 0.1N HCl (Y_1) in 0-10%, drug release in

pH 6.8 buffer (Y_2) in 70-80%, Hardness (Y_3) in 35-60N, Disintegration time (Y_4) in 1-20 sec and friability (Y_5) in 0-0.50% range were screened.

Figure 5a,b and c shows the overlay plot for dry polymer 91.5mg, 100mg and 115mg respectively kept constant. Figure 5d showed the overlay plot showing the optimized parameters suggested by DoE software to obtain the desired responses for formulation variables. The DS was established which was delineated in the green region in Figure 5d, the range of the process variable was, dry polymer of 91.5-115mg, PlasACRYL HTP 20 of 23-34mg and percentage of pellets of 25-42% of the point inside the green region.

Model predicts that process variables (represented by flag in Fig. 5d) with drug release in 0.1N HCl of 6.3%, drug release in pH 6.8 buffer of 76%, hardness in 48N, disintegration time in 17 sec and friability in 0.41% will have 100mg, 34mg and 35% of dry polymer, PlasACRYL HTP20 and percentage of pellets in tablet for formulation V4.





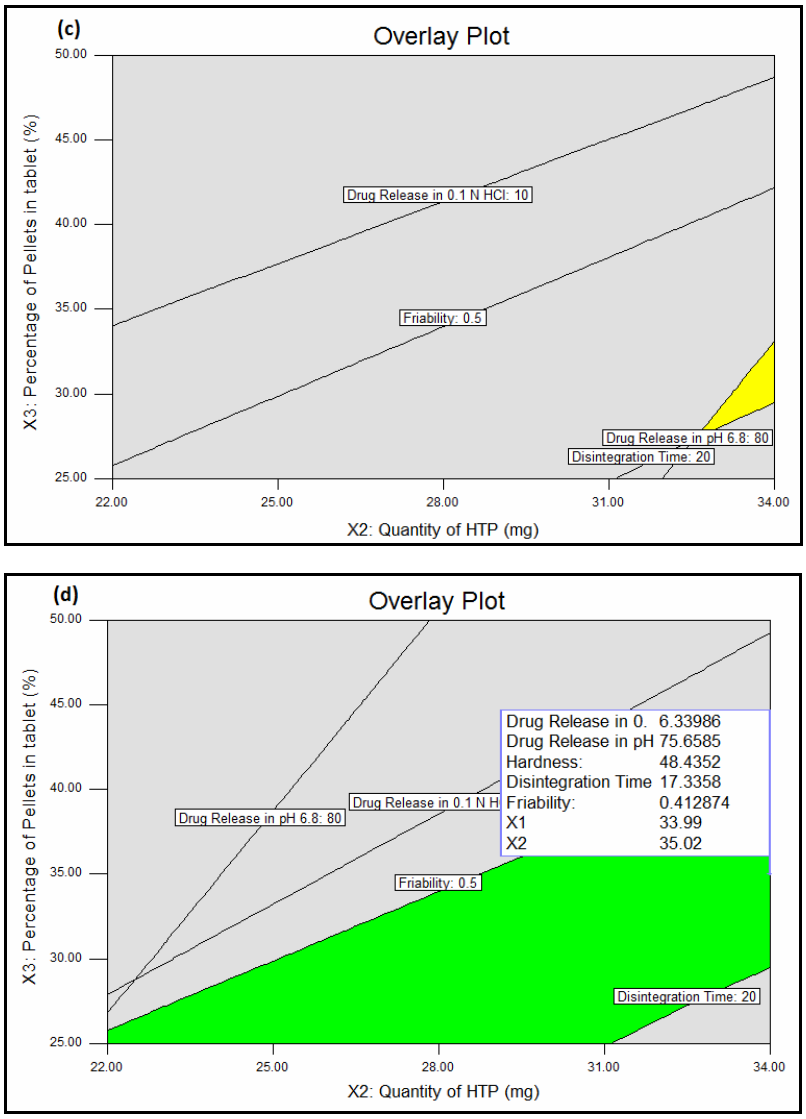


Figure 5. Overlay plot to prepared PTZ MUPS tablets comprised of the overlap region of ranges for the three CQAs using quantity of dry polymer of (a) 91.5mg; (b) 100mg; (c) 115mg and (d) Design space.

After prediction by software, the trial was taken with set of process variables suggested by model and characterized. As shown in Table 4 predicted and experimentally determined values for Y_1, Y_2, Y_3, Y_4 and Y_5 were comparable. These values were in very close agreement and established the reliability of the optimization procedure.

Table 4. Comparison between predicted and experimentally observed values for process variables

Responses	Predicted	Observed
Drug release in 0.1N HCl (Y_1)	6.3	6.0
Drug release in pH 6.8 (Y_2)	76	77
Hardness (Y_3)	48	47
Disintegration time (Y_4)	17	15
Friability (Y_5)	0.41	0.38

In QbD, robustness estimation is moved into method optimization for the definition of DS to ensure the CQAs values which were deduced from any working inside the DS are acceptable[40]. Once the DS is established, the validation becomes an exercise to demonstrate that the process will deliver a product of acceptable quality when operating within the DS[41]. No current regulatory document provides guidelines on how to estimate the DS

level[40] and no new concept exists to implement a control strategy in the pharmaceutical industry[42]. Based on the initial risk assessment and DS, a CS created with all three formulation variables was involved.

In Design Expert, the desirability response values were set $Y_1 < 10\%$, $70\% < Y_2 < 80\%$, $35N < Y_3 < 60N$, $Y_4 < 20$ sec, $Y_5 < 0.5\%$. In future, due to any reason formulation variables value need to change for commercial batches then based on DS it is possible without taking the prior approval supplement.

Determination of Control Strategy to prepared PTZ MUPS Tablets:

For ensuring a product of required quality of robustness and consistency during producing, ICH Q10 defines the control strategy as "a planned set of controls, derived from the understanding of current product and process that assures process performance and product quality"[4].

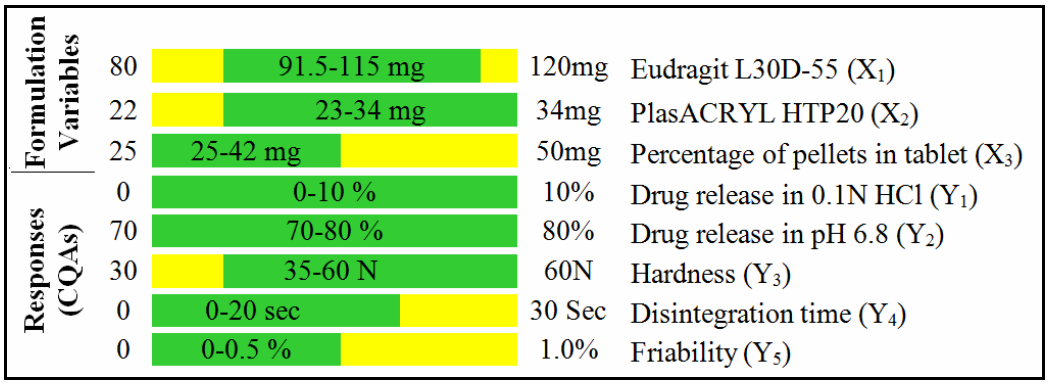


Figure 6. The control strategy for the preparation of PTZ MUPS tablets

The normal operating ranges is CS which is defined as the upper and/or lower limits for the critical material attributes. In the CS, the parameters were routinely controlled during production in order to assure the reproducibility[43]. The acceptable range of material attributes were determined based on the knowledge space from screening design and DS, the detail information was explained in Figure 6.

Quality risk management

Following completion of product development studies, a greater understanding of the risks to drug product quality associated with PTZ MUPS tablets which had been developed in design space which covered all validated range of formulation variables. Risk associated with formulation variables and mitigated discussed in Figure 7 based on validated design model and optimization study results. Using FMEA, the modes of failure can be prioritized for risk management purposes according to the seriousness of their consequences (effects), it can also be used to predict how frequently they occur and how easily they can be detected[44].

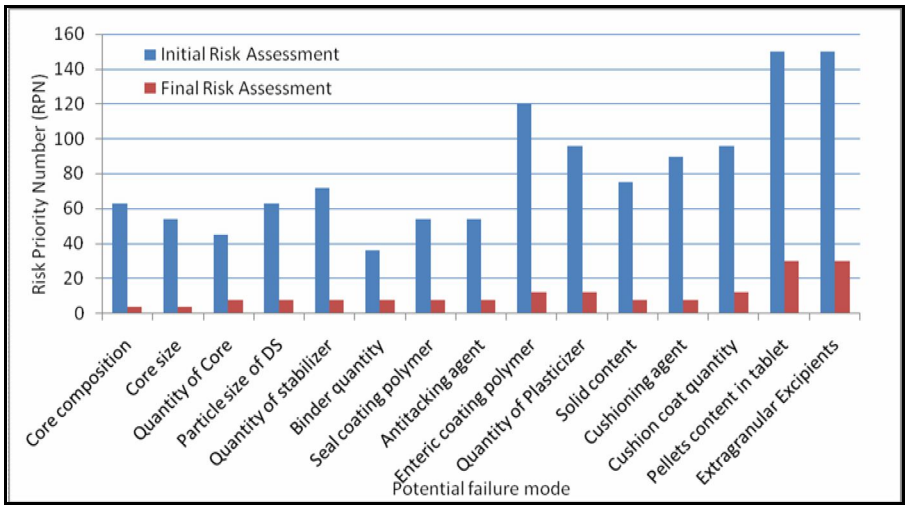


Figure 7. Pareto chart showing RPN scores for the operating parameters for PTZ MUPS tablet after risk mitigation.

Comparative dissolution

Pantoprazole delayed release tablet 40mg, Protonix® manufactured by Wyeth Laboratories considered as reference product to compare test formulation (V4). Related standard deviation (RSD) found at higher side at 10 and 15 min interval in stage II dissolution of reference product indicate that there was coating variation in tablet to tablet which was not found smooth in test formulation (V4). Comparative dissolution of reference and test formulation summarized in Table 5. Similarity factor i.e. f2 value found 56.5 indicated formulations V4 is pharmaceutically equivalent with reference product.

Table 5. Comparative dissolution of reference and test formulation

Time Intervals	PROTONIX®40 (B No: A20432)		Test Formulation (B No: V4)	
	Mean (%)	RSD (%)	Mean (%)	RSD (%)
Stage I: USP Type II/ 1000 ml 0.1N HCl / 75 rpm/120 min/37°C				
120 min	2	5.2	6	3.5
Stage II: USP Type II/ 1000 ml pH 6.8 Phosphate buffer/75rpm/60min/37°C				
10 min	8	9.4	57	4.9
15 min	28	7.6	64	3.8
30 min	79	2.1	76	1.7
45 min	92	1.1	89	1.1
60 min	98	1.8	95	1.9

Conclusion

From the above study it can be concluded that, QbD can be applied for pharmaceutical development of PTZ MUPS tablets, containing enteric coating polymer, ready mix plasticizer and cushioning extragranular excipients, which were reported to be reduce the cleavage of pellets during tabletting. Cause and effect diagram and FMEA analysis favors to identify critical formulation variables that affect PTZ MUPS tablets product quality. Full factorial design was applied to develop design space and determine the control strategy. The operating ranges, for robust development of PTZ MUPS tablet of desired quality, of enteric coating polymer, PlasACRYL T20 and percentage of pellets in tablet are 91.5-115 mg, 23-34 mg and 25-42% respectively. The release profile (DR) of tablet was found comparable to that of the target release profile (DR) of the marketed tablet. The optimization study were carried out and the result manifested that the predicted and observed observation were in a good agreement, which showed high degree of reliability of the model and resulted in the development of PTZ MUPS tablet formulation with optimum properties.

Declaration of interest

The authors report no declarations of interest.

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