ABSTRACT:

The purpose of the present work was to prepare Pantoprazole sodium sesquihydrate (PTZ) tablet prepared by multiunit particulate system (MUPS), applying QbD principle. PTZ is a popular proton pump inhibitor (PPI) however it has acid labile property, hence it is available in enteric coated form. The drug regimen prescribed for a period of one week to more than a year, based on disease condition. The MUPS tablets which specially designed for pediatric and geriatric patients, dissolve in mouth, can administer without water and without compromising the acid labile properties of PTZ. In vitro acid resistance characteristics of dosage forms was determined by performing dissolution in 0.1N HCl, which should be less than 10% for ideal system.

There are three variables involved in designing of MUPS tablets i.e. formulation variables, process variables and equipment variables. In formula designing of this research, pellets were prepared by suspension loading method where MCC pellets selected as core, level of stabilizer/alkalizer decided based on preformulation study, seal coating level optimized as per barrier requirement. Enteric coat was functional coat contained enteric coating polymer; Eudragit L30D-55 and additive mixture of plasticizer, anti-tacking agent and wetting agent; PlasACRYL HTP 20. The enteric coat with sufficient quantity of PlasACRYL T20 was inadequate to avoid cleavage of pellets surface during compression which overcome by applying cushion coat containing PEG 6000 over the enteric coated pellets. However, percentage of pellets in tablet blend determines the major crushing of pellets. Hence, design of experiment was performed using formulation variations; quantity of dry polymer (X₁), quantity of PlasACRYL HTP20 (X₂) and percentage of pellets in tablet (X₃). And the various responses, that to be observed or affecting were percent release of drug in 0.1N HCl (Y₁), percent release in phosphate buffer pH 6.8 (Y₂), hardness (Y₃), disintegration time (Y₄) and percent friability (Y₅).

No design was framed for those formulations where X₁ was below 91.5 mg and X₃ was above 42 percent to prepare Pantoprazole multiunit particulate tablets. The desired quality or operating ranges, for robust development of Pantoprazole multiunit particulate tablets of were decided as X₁ between 91.5-115 mg, X₂ between 23-34 mg and X₃ between 25-42% respectively. Drug release profile of the final selected formulation V4 found comparable with reference product. Not only did the ternary
A 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.

Comparative dissolution of prototype formulation and reference product (Pantoprazole delayed release tablet 40mg, PROTONIX® 40mg) performed in release media as per USP. To know the \textit{in vivo} performance by in vitro dissolution study, dissolution performed on biorelevant media. Comparative biorelevant dissolution performed in stage I (FaSSGF pH 1.6) followed by stage II (FaSSIF pH 6.5). The dissolution profile of both the samples was comparable in biorelevant media. It was suggested that prototype formulation has good potential for bioequivalent to reference product.

Enteric coating was the critical process. The critical process parameters (CPP) were identified based on initial risk assessment method. A full factorial design was applied to develop design space and determine control strategy for pantoprazole enteric coating process, have promising yield, assay and reduced process time. The coating process variables studied were air volume ($X_1$), spray rate ($X_2$) and atomization air pressure ($X_3$), versus percentage fines ($Y_1$), percentage agglomerates ($Y_2$) and assay ($Y_3$) as responses. The pellets were coated in Wurster and characterized for assay, dissolution, scanning electron microscopy and loss on drying. When $X_2$ at low level and $X_3$ at high level, spray drying increased hence fines increased while $X_2$ at high level and $X_3$ at low level, agglomeration increased. The optimization performed to decide level of $X_2$ and $X_3$ for fines and agglomerated free process. The operating ranges, for robust coating process of desired pellets yield and quality, $X_1$, $X_2$ and $X_3$ were 46-58 CFM, 6-9 g/min and 1.1-1.3 bar respectively. In scale up of pellets, physical and chemical parameters reproduced based on process ran as per scale up factor calculation. It was concluded that a promising pellets coating process was successfully designed using QbD approach and successfully scaling up was possible based on complete optimization of process variables, understanding of risk associated with variables and implementation of scale up factor calculation provided by vendor.

Enteric coated Pantoprazole pellets were compressed to oro-dispersible tablet for geriatric and pediatric patients for easy administration. The risk related to compression process variables were identified, assessed and mitigated. A full factorial
design was applied to develop design space and determine control strategy for compression process, which were developed, have promising chemical and physical results. The compression process variables studied were pre-compression force ($X_1$), main compression force ($X_2$) and turret speed ($X_3$), versus affecting hardness ($Y_1$), disintegration time ($Y_2$), friability ($Y_3$), weight variation ($Y_4$), content uniformity ($Y_5$), drug release in 0.1N HCl ($Y_6$) and assay ($Y_7$) as responses/Critical quality attributes (CQAs). Response surface graphs depicted that $X_2$ had more impact on CQAs than $X_1$. Design space plot revealed that tablet CQAs were within limit when $X_3$ maximum 44 rpm and $X_2$ in the range of 10 to 12.5 kN. Scale up performed on commercial scale compression machine of same make that of lab scale showed reproducible physical and chemical parameters.

It could be concluded that a quality Pantoprazole oro-dispersible MUPS tablet was successfully designed using QbD approach to compression process variables.