EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 3
220-227
Year: 2022

QUALITY BY DESIGN (QBD): APPLICATION OF QBD IN PELLETIZATION

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Article Received on 24/12/2021 **Article Revised on 14/01/2022** **Article Accepted on 04/02/2022**

ABSTRACT
The primary idea of QBD is "The Quality cannot be examined into the product; however it must be constructed into it." Quality through design is the cutting-edge technique for the true standard of pharmaceuticals. It describes use of Quality through design to make certain grade quality of Pharmaceuticals. In this review paper, the Quality through design and a number of its parameters are described. This review article involves the benefits of QBD, steps involved in the QBD process and the applications of QBD. The compiled data from various research articles explains the importance as well as future need of QBD parameters. QBD plays a major role in screening of various formulated product, it is not only saving the time but it is proven beneficial for the economy of various manufacturing companies. Now a days emerging pharmaceutical companies are developing their interest towards QBD studies to depict factors interfering in the results. QBD makes it easier to achieve the best suitable batch in pharmaceuticals. QBD has its own contribution to the drug layout, improvement, and manufacture of extraordinary drug merchandise. It is better to know the quality target product profile (QTPP) for identification of critical quality attributes (CQA). This article will be beneficial in predicting CQAs, CMA etc. QBD involves the application of different design tools such as Plackette Burman, Boxe-Behnken, Central Composite, RSM etc. Hence Quality through design is totally a novel technique for making advancement in the field of medicine, which may be stated as a remedy with pharmaceutical advances.

KEYWORDS: Pellets, FMEA, Ishikawa Plot, CQA, ANOVA.

INTRODUCTION
The aim of pharmaceutical development is to style a prime quality product and its manufacturing process to consistently deliver the intended performance of the merchandise. The data and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the look space, specifications, and manufacturing controls. Information from pharmaceutical development studies are often a basis for quality risk management. It is important to accept the fact that the quality can never be tested into products, such as quality should be built-in by designing the different Changes in formulation and development processes during manufacturing and lifecycle management should be considered as opportunities to realize additional knowledge and further support establishment of the design space. Also, addition of relevant knowledge gained from experiments giving unexpected results also can be useful. Design space is suggested by the applicant and is subjected to regulatory assessment and approval. Working within the design space isn't considered as a change. Movement out of the design space is taken into account to be a change and would normally initiate a regulatory post approval change process.[1,2]

Definition [ICH Q 8(R1)]
A systematic development approach that starts with predefined goals and emphasizes product and process understanding as well as process control supports sound science and quality risk management.

Benefits of QBD
- QBD is good Business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- QBD is good Science Better development decisions
- Empowerment of technical staff

Opportunities
- Efficient, agile and flexible system

- Increase manufacturing efficiency/ reduce costs and project rejections and waste
- Build knowledge domain base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management

Steps involved in Quality by Design products

1. Development of latest molecular entity
- Preclinical study Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

2. Manufacturing
- Design Space
- Process Analytical Technology
- Real time internal control

3. Control Strategy
- Risk based decision
- Continuous Improvement
- Product performance

Seven steps of quality intentionally begin plan

1. Hire an independent Quality intentionally expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality intentionally workshop with all of your personal.
4. Review the Draft an implementation plan, timelines and estimated costs.
5. Assign the resources (or contract out).
6. Retain the independent expert as your "Project Assurance" advisor.

Applications of Quality By Design (QBD)

Quality by Design (QBD) – an extensive systematic approach to pharmaceutical development and manufacturing Advancement bounded by the the pharmaceutical development and manufacturing by QBD is often explained against traditional approach In Pharmaceutical Research and Development To design a quality product and a manufacturing process to consistently convey the intended performance of the product In life cycle management Continual improvement enabled within design space.

This article contains research review on applications of QBD in design of pellet dosage formulations.

Satish k. Mandlik *et al, (2020)* has done a research on "Implementation of quality design (QBD) approach in formulation and development of ritonavir pellets using extrusion spheronization method.[2]

Objective: Ritonavir have anti-retroviral activity and is used for HIV-AIDS therapy. The motive of this research work was to carry out the standard intentionally (QbD) approach in formulation of ritonavir sustained-release pellets by industrially pertained extrusion Spheronization technique.

Methods: Pellets were formulated by extrusion spheronization method and evaluated for physicochemical properties. At first, on the basis of prior knowledge Quality Target Product Profile (QTTP) elements were identified and further Critical Quality Attribute (CQA) elements were defined. Risk assessment (RA) was completed by two tools as failure mode and effect analysis (FMEA) and fishbone diagram (i.e. Ishikawa plot). Placket Burman design was implemented as a screening design using seven high-risk factors (such as spheronization speed, spheronization time, extrusion speed, drying method, PVP K 30, cross povidone, and solvent). Optimization study was accomplished by 2^3 full factorial design with three critical factors as (spheronization speed, extrusion speed and PVP K 30). The in-vitro drug release was studied and considered in both gastric and intestinal fluids for 12 h using USP I apparatus. Control space was confirmed and established for the sustained release pellets.

Results: Among all batches obtained in 2^3 full factorial design, batch R7 was found to be effective with carr's index value of 5.281, percentage yield of 69.6%, time required to release 50% drug was 8 h and percent drug release after 12 h was found 83.132 %, R7 batch was selected as optimized batch. Statistical analysis showed model terms were significant.

Conclusion: QbD is an important a part of the fashionable approach to pharmaceutical quality. This current study demonstrated how QbD approach can be applied toward the development of a formulation of ritonavir SR pellets. This study teaches the use of QbD including an emphasis on the importance of the target product quality profile in a quantitative performance target for QbD. Fish-bone diagram and FMEA analysis were used to identify critical formulation and process parameters that affect ritonavir sustained-release pellets product quality. Next, the Plackett-Burman and 2^3 factorial design were used for screening the significant factors and optimizing the variables range, respectively. The final aim of this approach was to achieve Design space. Lastly control strategy was defined. It could be concluded that sustained-release pellets were successfully designed using QbD approach.

Shuling Kan *et al, (2014)* has done research on "A quality by design (QBD) case study on enteric coated pellets: screening of critical variables and establishment of design space at laboratory scale.[1]

The study attempts to organize naproxen enteric-coated pellets (NAP-ECPs) by fluid-bed coating using QbD principle. Risk assessment was performed initially by using failure mode and effect analysis (FMEA) methodology. A Plackette Burman design was then used for valuation of the most important variables which were affecting enteric-coated pellet characteristics. A Box

Behnken design was subsequently used for investigating the main, interactive, and quadratic effects of these variables on the result and response. With FMEA they discovered that eight factors should be considered as the high/important risk variables as compared with others. The results of acid resistance and cumulative drug release were taken and considered as critical quality attributes (CQAs). Pareto ranking analysis indicated that the coating weight gain (X7), triethyl citrate percentage (X1) and glycerolmonostearate percentage (X2) were the most notable factors affecting the selected responses out of the eight high-risk variables. Optimization with response surface method (RSM) further fully clarified the relationship between X7, X1, X2 and CQAs, and design space was established based on the constraints set on the responses. Due to the acute coincidence of the anticipated value generated by model with the detected value, the accuracy and robustness of the model were confirmed. It might be concluded that a promising NAP-ECPs were successfully designed with respect to QbD approach during a laboratory scale.

Conclusion: They concluded that the study demonstrated how the QbD approach can be used for the development of the ECPs preparation. Fish-bone graph and FMEA analysis were used to identify critical formulation and process parameters that affect ECPs product quality. And on the other hand the Plackette-Burman and Boxe-Behnken design were used to screen the many factors and in optimizing the variables range, respectively. The main motive of this research was to achieve a process model of the ECPs preparation, thus a DS can be established based on it, and a CS could be further obtained. Confirmation tests were carried out at three levels i.e. low-level, medium and high of the variables and the results manifested that the prediction and experimental observation were in a good agreement, which confirmed the accuracy and robustness of the model.

Dharmesh b. Patel *et al, (2018)* has done research on "Design and Development of extended release pellets delivery of desvenlafaxine by employing principles of quality by design.[3]

Desvenlafaxine succinate (DV) belongs to serotonin-norepinephrine reuptake inhibitors (SNRIs). The study regarding DV was attempts to formulate extended release pellets of DV. The pellets were formulated by extrusion spheronization technique and suitable extended release coating was applied by fluidized bed coater. Various principles of QbD (such as QTPP assessment, Risk estimation matrix, screening design, factorial design) were used for optimization of the pellets. In coating composition, % weight gain and % EC were considered as independent variables and % drug release at 2, 4, 8, 12 and 20 hrs were detected as responses. The drug was found compatible with proposed excipients which was proved by FTIR and DSC study. Quantification of DV was done via UV spectrophotometry method at 224 nm. Results of physicochemical study suggested pharmacopoeial compliance of DV pellets. Drug release kinetics study revealed that drug release profile was best suited with Weibull model. The intactness of coating on pellets was determined by SEM and found appropriate. The outcome of short term stability study of DV pellets confirmed physical and chemical stability. Thus, they concluded that developed formulation of ER pellets can be formulated for prognosticating approach for once a day dosing of DV for continuous release in treatment of depression.

Conclusion: From the exhaustive study on formulation and development of DV ER pellets, it can be concluded that QbD and its tools assisted for proper development in systemic way. Role of EC was found superior than other factors for achieving desired release and coating composition was remained intact in dissolution media and also in the presence of 10% V/V alcohol. So, proposed drug delivery system can be suited best for once a day dosage regimen for DV and similar drugs and depression alike conditions.

Bala Vishnu Priya Mukkala *et al, (2017)* has done research on "Process optimization of methylphenidate hydrochloride extended release pellets by QBD.[9]

Objective: The aim of this research work was to optimize the method of Methylphenidate Hydrochloride (HCl) Extended release (ER) pellets supported by Quality by design (QbD) attributes.

Materials and methods: They used Wurster (Bottom spray fluid bed coating) process to develop ER pellets of Methylphenidate HCl. Impact of assorted process variables on drug layering process were assessed by using statistical interpretation like ANOVA. A face centered central composite design (CCD) was employed to work out the effect of independent variables (such as product temperature, atomization gas pressure fluidization air volume, and spray rate) on dependent variables (like Fines, agglomerates, coating efficiency and assay). Fabricated pellets were used for various physicochemical parameters and stability studies.

Results: Optimization studies were accomplished by fitting experimental results to the software program (i.e. Design expert software). The design space for process parameters and its impact on % fines, % agglomerates, coating efficiency and assay was developed. From the derives results, 40°C ± 2°C as product temperature, 0.8-1.0 kg/cm^2 as atomization Air pressure, 45-60 CFM as fluidization air volume and 2-6 g/min as spray rate were selected because of the operating ranges for robust coating process, desired yield and quality of the product. The drug release from the optimized formulation obeyed first order kinetics and fickian diffusion process. There is no significant change observed during stability.

Conclusion: Methylphenidate HCl ER pellets generating a biphasic release profile from single core were

successfully fabricated by fluid bed coating technology. Impact of varied process variables on drug layering process was assessed by using response surface methodology. This investigation revealed that independent variables had a significant influence on the measured responses. The quantitative effect of these factors at different levels on responses might be predicted by polynomial equations. The Linearity determined between the actual and predicted values of the response variables indicated that analytical ability of the selected design was appropriate. From the determined results, 40°C ± 2°C as product temperature 0.8 -1.0 kg/cm^2 as atomization air pressure, 45-60 CFM as fluidization air volume and 2-6 g/min as spray rate were selected as the working ranges for robust coating process, desired yield and quality of the product. The optimized batch showed 100.2% assay and drug release was well within the predetermined specifications [Similarity factor (F2) value – 68]. Micrometric properties of these pellets exhibited excellent flow properties, which were crucial to get the uniformity of dosage units in capsule filling.

Bala Vishnu Priya Mukkala *et al, (2018)* has done research on "Development of fenofibric acid delayed release pellet: optimization of process variables in fluid bed process."[8]

The objective of this study was to optimize and estimate the values of Fenofibric acid delayed release (DR) pellets.The Wurster (Bottom spray fluid bed coating) process was manipulated to develop the Fenofibric acid delayed release pellets. Their study assessed the impact of assorted process variables on drug layering by using statistical interpretation like ANOVA method. A face centered middle composite design (CCD) was introduced to review the effect of independent variables (like product temperature, atomization air pressure fluidization air volume and spray rate) on dependent variables (agglomerated, coating, Fines, efficiency and assay). The Fabricated pellets were identified for various Physico-chemical parameters and stability studies. Optimization study was carried out by fitting experimental results to the software program (Design expert). The design space for process parameters and its influence in accordance to % fines, % agglomerates, coating efficiency and assay was estimated. From the attained results, 40°C ± 3°C as product temperature, 0.8 - 1.2 kg/cm^2 as atomization air pressure, 50 -65 cfm as fluidization air volume and 2-6 g/min as spray rate was determined to be the operating ranges for robust coating process, required yield and quality of the product. The drug release from the studied formulation followed first order kinetics and controlled by non-fickian transport. There was no remarkable change found during stability. It was concluded that the face centered central (middle) composite design facilitated the method optimization of Fenofibric acid DR pellets. Hence the successful formulation and development of the fenofibric acid DR pellets was carried out via bottom spray fluid bed coating (Wuster) respectively.

Conclusion: Fenofibric acid delayed release pellets were successfully fabricated by fluid bed coating technology. The impression of various process variables on drug layering process was performed by using response surface methodology. This explored study revealed that independent variables had a significant impact on the measured responses. The quantitative effect of these factors at different levels on responses could be speculated by polynomial equations. Linearity observed between the actual and predicted values of the response variables indicated that analytical ability of the selected Design From the obtained results, 40°C ± 2°C as product temperature, 0.8-1.2 kg/cm^2 as atomization air pressure, 50-65 cfm as fluidization air volume and 2-6 g/min as spray rate were determined as the operating ranges for robust coating process, desired yield and quality of the product. The optimized batch showed 98.7% assay result and drug release was under the known specifications (Similarity factor (F2) value -7). Micromeritic properties of those pellets exhibited excellent flow properties, which are crucial to achieve the uniformity of dosage units in capsule filling. The optimized formulation can be assessed as an alternative to the marketed formulation. Therefore, the applicability of response surface methodology to optimize the method variables within the fabrication of Fenofibric acid DR pellets is apt enough.

Satyananda Patra *et al, (2018)* has done research on "Pelletization of iron ore fines with parameter optimization through box – behnken design."[7]

Using a Box-Behnken design, experiments are considered better over full factorial design in that the same output information can be obtained with less number of experiments. Box-Behnken design was used in the present study and the product pellet characteristics of d50.

The research study was concentrated on optimization and characterization of process parameters during green Pelletization in order to estimate the importance of green pellets in indurations (hardening of the soft tissues of body). Three level Box-Behnken design along with Response Surface Methodology (RSM) was carried out for modeling and optimization of parameters like d50 yield of +9mm pellets, MDN and GCS of pellets. Beneficiation studies were carried out and hence the optimum condition attained permanent strength green pellets and they were at d50 of 13.8mm, % yield of +9mm pellets of 93.29% MDN of 17.3 and GCS of 1.94kg/pellet were obtained at the moisture (M) of 14%, rotation (R) of 44.39rpm and betonies (B) of 0.54 wt.

Conclusion: This study involved three-level Box-Behnken factorial design combined with a RSM for the aim of modeling, optimizing and characterizing three operational parameters for ore green pelletization. The Mathematical model equations were referred for all the responses separately by using sets of experimental data and a mathematical software package (MINITAB 17 Trial). It was therefore concluded that best results of

13.8mm, %yield of +9mm pellets of 93.29%, MDN of 17.3 and GCS of 1.94kg/pellet were estimated at the M of 14%, R of 44.39rpm and B of 0.54wt%

Michal Holubcik *et al, (2012)* has done research on "Optimization of the production process of wood pellets by adding additives."[20]
In this work authors described the probabilities for improving efficiency of wood pellets production. The introductory is dedicated to analyzing the properties of wood pellets combustion and production of pollutants when combusted it. The assembly of wood pellets and used pelleting machines was analyzed. The most important task of this work was to introduce the efficiency of pelleting lines and decrease of the wood pellets production as fuel paying attention on the implications of adding additives. The results of experimental measurements and properties of wood pellets with different additives were presented within the final part.

Conclusion: Incorporation of additives to wood sawdust reflected some properties of wood pellets. Moisture produced by pellets was almost similar, Ranging from 541- 842 %. Comercially available pellets on the market have moisture around 11%.The tested sawdust were subsequently humidified, difference may arise due to errors in weighing the starting material and additional moisture. Another cause may be insufficient mixing of material and then selecting unrepresentative sample.

The density of formulated pellets was from 1,139-1,302g $cm^{-3}$and it was estimated that the lowest density was reached in the case pellets with 5% addition of vegetable oil. It was observed that the additives with significantly higher density decreased the density of produced wood pellets, additives were likely to affect the pressing process when lignin may not be adequately melted and the pellets were less compact. Values may be partially deformed by inaccurate measurement of the dimensions given the imperfect cylindrical shape of pellets.

Bulk density of regular wood pellets found was about 650kg $.m^{-3}$. For comparison bulk density of produced pellets ranges from 617 to 695 $kg.m^{-3}$. These values were dependent on the length of the pellets and their ability to fill a volume. The determined values may be influenced by improper filling of the volume of the container.

The calorific value is the most important property of the pellets. Pellets reach the calorific value from 17 to 21 $MJ.kg^{-1}$, depending on humidity. Produced wood pellets with additives have calorific value from 18,372 to 19,584$MJ.kg^{-1}$. Almost all samples of pellets have a calorific value above the 185 $MJ.kg^{-1}$ the exception being only pellets with 0.5% addition of limestone. This deviation may be due to the higher moisture samples. Given the results of samples calorific value is possible to conclude that a small amount of additives has a great influence on the calorific value of produced pellets. During the measurement, errors may be arise due to in-accurate weighing of water into the calorimeter.

The disintegration time of pellets in water isn't an appropriate meticulous method of determining the standard of a wood pellets, but it's okay to check quality of compassion between each sample pellets. It is said that vegetables and gasoline negatively affects the standard of pellets. 5% amount pellet incorporation into vegetables oil is the exception among the opposite sampleshigher amounts of oil probably declined the ingress of moisture into the material of pellets. Effect of cornstarch was confirmed as replacement of lignin and might be as an additive in material that have low natural lignin effect of limestone within the water test had an identical effect then corn starch.

Also addition of additives to wood sawdust reflected input power of pellet mill. The lowest electric power consumption has been achieved in the production of pellets from sawdust with 5% addition of vegetable oil. The significant increase in electric power. And thus higher friction of the input material pressed through matrix was in the production of wood pellets with 1% addition of urea and sodium carbonate. Assumption of reduction of electric power by using cornstarch as an additive was not confirmed when this value slightly increased.

The maximum cost savings on electricity of pellet mill is achieved by using lubricant additives. cost saving is dependent on the amount of lubricant additives and can reach nearly 15%. Compared with costs in the production of wood pellets from clean sawdust (assuming a maximum of 5% the amount of added additives). When using additives affecting the properties of wood pellets. In particular, formation of pollutants has been achieved the highest increase in electricity costs.

In practice, with a better dosage and mixing of the input material, the amount of was determined from 0.5 to 1%, depending on the weight of clean sawdust, this explained that the cost savings on electricity consumed by pellet mill could outreach a value of 6%.

Taking into account of all cost, the planned 6% reduction of input power will be reduced to 0.36% of total production cost. This value should be added to the saving of raw material because additive is part of raw materials entering to the pellets mill, thus saving on material (0.57%) should be added to the total cost (savings from the total cost is 0,29%). It follows that the maximum saving on production costs may be approximately 0.65% (the estimated amount of additive from 0.5 to 1%).

This research was solved with external company with pelleting line with pellets production of 2 tons per hour. Its main objective was to reduce the operating costs of the production of wood pellets all analysis of costs were used from this company.

Gurinder Singh *et al (2012)* has done a research on "Optimization of pellets containing solid dispersion prepared by extrusion/spheronization using central composite design and desirability function."[6]
Furosemide is considered as a category of IV biopharmaceutical system drug having poor water solubility and low bioavailability because of the hepatic first-pass metabolism it is believed to have half-life of two h. To induce control over the above drawback, this study was carried to formulate and evaluate the pellets containing furosemide solid dispersion (SD) with the aim of oral administration prepared by extrusion/ spheronization SD of furosemide prepared with Eudragit (L-100) polymer at a drug-to-polymer ratio of 1:2 by employing a solvent evaporation method and characterized. Further, Microcrystalline cellulose pellets containing SD were consequently prepared employing a lab scale extrusion /spheronization and evaluated for in vitro drug release studies. The influence of process parameters used during extrusion/spheronization on the pellet properties was also studied using 2-factor, 3-level central composite design so on to enhance the merchandise quality. Additionally the desirability function approach was applied to accumulate the preeminent compromise between the multiple responses. Pellets containing solid dispersion (PSD) were prepared using optimal parameter settings demonstrated 88.52± 0.69% of the drug was released in an exceedingly sustained release manner till 12 h. In Vitro drug release data were fitted to varied release kinetics models to review The mechanism of drug release. Drug release from the PSD followed zero-order and Higuchi's model both, studied parameters had great influence on the responses. PSD showed augumentation within the drug release profile till 12 h. The ultimate optimized formulation was obtained by encapsulating best SD formulation within the pellet core to release the drug within the foremost soluble form in stomach and a sustained fashion in intestine.

Conclusion: Successful dissolution rate improvement of furosemide was obtained using SD prepared with Eudragit L-100 by a solvent evaporation method. Furosemide was presented as an amorphous state in the SD at a drug- to –polymer ratio of 1:2 (w/w) and released almost 30 times faster than the pure drug. PSD showed high content uniformity and showed a SR profile with approximately 88.521% of drug was released at the end of 12 h. product properties including the dissolution profile and percentage yield of the desired size fraction were improved by using the optimal parameter setting and the results showed a good agreement with the prediction of the models. The method used to prepare SD of furosemide in this study is relatively simple and safe, because of the absence of specialized equipment organic solvent Kneading time and spheronizer speed were significant parameters which influence the pellet characteristics complicatedly during the high palletization process. These parameters could be optimized successfully by a CCD.

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Haralds Vivita *et al (2016)* has done research on "Process optimization for pellets production."[5]
Nowdays, it's necessary to form industries more and more energy efficient. After the study pellets production, energy consumption improvements were strongest effects to be considered. Optimization methods for drum dryers and combined heat and power plants (CHP) are offered during this paper , as these are the most thermal energy sources in pellets production Drum dryers are used to dry sawdust used for pellet production, it's importanat to look through at the efficiency of the drying process and also the problems caused by human factor. A technique of automatic drum dryer implementation is applicable within the paper. However, CHP can have proved to be more efficient for pellet production with reduced CO2 emmissions when considered with drum dryers. CHP is often divided, supported the patron type as CHP in heating system system and industrial CHP. The previous provides thermal energy for consumers in cities, and therefore the latter provides it for local Factories And industrial group. There is decline in thermal energy consumption over the summer, giving a chance to use the remaining thermal energy for cooling needs.Finding solutions to extend heat capacity is vital to extend electricity production from CHP and improve plants economics efficiency. The result offered within the paper is remaining thermal energy use in absorbent coolers needs.

Conclusions: The authors concluded that the regulation system was accustomed to improve the efficiency of the drum dryer furnace. Its an optimization methods that ends up in declined human factor effects on the drum drying process and a more efficient consumption of energy and resources. This might result in increase in pellet production amounts.Within the future, monitoring of the instrument panel data would help to obtain precise conditions for more practical combustions.

- Full combustion of fuel material are going to be provided
- Combustion flue gas will burn, therefore achieving full capacity of the furnace
- Process happening within the woodchip furnace are easily controlled
- Determined by automatic system, secondary air feed system will work more effectively
- Furnace automated system will provide steady furnace operation by controlling several combustion parameters at the similar time period.

Traditional CHP will be transformed into TP when there's a cooling demand. A case study was performed on CHP that has energy for wood factory. Existing data were used for modelling of calculations. Calculation showed that payback period for absorption coolers cost is smaller amount than 6 years. The utilization of those coolers would turn CHP into TP and would supply extra electricity over the summer. thanks to increased thermal energy load that might also contribute to savings from fuel.It is necessary to perform a case study in similar CHP that includes a need regular coolings conditions, to match results and procure actual data about CHP and TP performance.

Shelar Vishwas *et al (2018)* had done research on "Formulation optimization of promethazine theoclate immediate release pellets by using extrusion-spheronization technique."[4]

Objective: The main objective of this study was to formulate and optimize a drug via extrusion spheronization technique. Promethazine theoclate is an anti-histaminic drug and comes under BCS Class II classification .This drug is preferred for the treatment of kinetosis and postoperative emesis. The head objective of the research work was to formulate and optimize immediate release pellets of promethazine theoclate by implementing the extrusion-spheronization technique to supply immediate release dosage form suitable for treatment of nausea and vomiting associated with motion sickness and post-operative conditions.

Methods: Microcrystalline cellulose (MCC) and maize starch were used as filler and disintegrant, respectively, in the formulation of promethazine theoclate immediate release pellets, along with additional excipients. Using a 32 factorial design, a pellet formulation was further refined for bulk density, disintegration time, and percent drug release after 10 minutes. Differential scanning calorimetry (DSC), surface morphology using scanning microscopy (SEM), and other physicochemical parameters were also investigated in the formulations.

Results: Optimised pellet formulation contains 2.5:4.5:1 ratio of MCC: Corn Starch: Drug and spheronization time of 60 seconds showing highest percent yield of 78% and immediate drug release of 100.52±0.65% after 10 min.

Conclusion: The goal of this study was to design and refine promethazine theoclate loaded quick release pellets as a multiparticulate drug delivery system that could be given after being filled into a gelatin capsule.

The formulation was optimised using a 32-factorial design and an investigation including polynomial equations, surface response plots, and counterplots generated during the research. The optimised formulation (IX) had the maximum percent yield of 91.4, a bulk density of 0.580.02 g/ml, and good flow parameters, including a 24.560.02° angle of repose, 0.580.35% friability, and a disintegration time of 21.05 seconds. After 10 minutes, the particle size of the improved formulation was found to be 1.290.37 mm, with abortifacient release of 100.520.65. Independent variables, such as MCC concentration and Corn starch concentration, had a significant effect on dependent variables, such as bulk density, disintegration time, and percent drug release after 10 minutes, which were critical parameters in terms of dosage, disintegration, and drug release when pellets are to be delivered into the capsule. The improved formulation's percent drug release (IX) was found to be comparable to that of the marketed formulation (Avomine Tablet). After 30 days of storage, the optimised formulation (IX) was shown to be stable at 40 °C and 75 percent RH. Promethazine theoclate pellets developed in this work are frequently utilised as an alternative to tablet dosage forms for the treatment of kinetosis and post-operative emesis because they provide quick drug release.

RESULT AND DISCUSSION

QBD is an essential part of the modern approach to pharmaceutical quality. This review article demonstrated how QBD approach can be applied toward the development of formulation of pellets. From the above study it is concluded that QBD gave the satisfactory results in various studies. QBD approach proved best for the pelletization technology. Screening of various parameters such as Critical quality attributes (CQA), Critical material attributes (CMA), and Quality target product profile (QTPP) using Plackett-burman, Box-Behnken, Ishikawa plot and factorial design were accomplished by fitting experimental results to the software program.

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