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QUALITY BY DESIGN APPROACH FOR THE FORMULATION OF DUAL RELEASE DRUG DELIVERY SYSTEM: A CHRONOMODULATED APPROACH

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Keywords:

Chronomodulated drug delivery, Quality by design, Dual Release Tablets, Risk assessment, Worldwide patents, Biolgical Rythm

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ABSTRACT: The focus of the current article is to prepare the chrono-modulated dual release formulation using various optimization techniques. The conventional formulations as the Controlled Release Drug Delivery System (CRDDS) are not effective in the chronomodulated formulation. The advancement in research and development in CRDDS leads to the formulation of chronomodulated formulations. Dual release tablets are those in which two drugs are given in a single tablet in different layer as to avoid the incompatibility problem or single drug is given in two different layers as maintenance dose and loading dose. The formulation is fruitful in various diseases such as diabetes, arthritis, asthma, etc., and provides compliance to the patient as a patient has no need to wake up during night hours to take the mediation. The Quality by Design (QbD) techniques is used to make the formulation as much as safe and efficacious. By applying the QbD, product variability is reduced and leads to quality improvement, risk reduction, and production enhancement. In conclusion, chronomodulated drug delivery system using QbD tools can be effective for dual-release formulation.

INTRODUCTION: Gout is arthritis that occurs when too much uric acid accumulates in the body; acute gout occurs when there is an accumulation of too much uric acid in the body that is during the midnight to early morning. This happens due to too much uric acid in the blood, and it leads to the formation of crystals in one of your joints. The big toe is the most common place to happen and symptoms are sudden and severe pain. There is also a risk of a patient for low purine intake during last 24 h prior to attack. When breaking down, purine body produces uric acid. Certain foods are high in purine including organ meat, seafood, and alcohol.

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The measures that prevent gout flares, especially at night, maybe more effective. Thus an ideal drug delivery, in this case, would be to administer the drug at bedtime, but the release of drug will take place from midnight, through early hour in the morning and then during the day [1, 2, 3].

From ancient times, daily rhythm has been observed between plants and animals. In the early fourteenth century Alexander, the great found that there is certain tree whose leaved opens during day time and closes during the night and these kinds of the tree shows maximum rhythmicity. The first experiment on biological rhythm was conducted by French Astronomer Jean Jacques d'Ortous. After that, it has been confirmed that insect uses photoperiodic information for growth in hormony with seasons [1]. The two scientific concepts that specifically study when any drug produce best therapeutic effectiveness, as well as least side

effects in human as well as insect, are chronopharmacology and chronotherapeutics. To know the chronotherapy of various diseases, the biological rhythms have been identified, and symptoms during circardic variation in the disease could be the best marker to determine at what time the drug should be administered. Out of various therapeutic properties, pain is one. Pain is induced when the circardic variation occurs in the body [4]. So in order to put up different pathological conditions, various possible routes available are used for the administration of drug [5].

In these days all the developed and developing countries are moving in the field of combination therapy for treating different disease or disorders that require long term treatment such as hypertension, diabetes, cardiovascular diseases *etc*. [6] Among all the dosage form the oral dosage form is 50-60% accepted and it is preferred route because of pain avoidance, ease of administration, accurate dose and flexibility in formulation. Conventional dosage form has attribute liability to repetitive dosing, and the absorption window is not predictable, which leads to vast fluctuation in drug concentration in bloodstream and tissues. This dynamic that is repeated dosing interval and irregular absorption lead to the new concept that is controlled drug delivery system. When different polymers prepare a formulation in different layers than this will allow manipulation over one or more than one rate-controlling polymer, thus enable different types of drug delivery with one or more than one drug, *i.e.*, by employing different types of pH-dependent polymer, the drug may be released at pH bolus and at a controlled release rate.

The aim of designing and preparing a sustained or controlled release drug delivery system is to reduce the dosing frequency and to enhance the effectiveness of the drug by localizing it at the site of action. The objective of a controlled release drug delivery system is to enhance the safety and efficacy of the drug as well as enhance patient compliance. But all these advantages cannot be achieved by a controlled release drug delivery system because there is a deficiency in releasing the initial bolus dose dumping and failure to achieve site-specific drug delivery. Also, there is a rapid disintegration in the immediate-release drug delivery system and thus achieve instant drug release. But there is a fluctuation in plasma drug concentration-time which leads to a reduction of drug effectiveness with enhanced side effects. Thus it is necessary to administer the DDS bid or tied to compensate for the reduced plasma concentration because of metabolism and excretion. But to maintain the optimum drug concentration in the therapeutic window constant plasma drug concentration-time profile is required. However, once-daily dosage form cannot be achieved easily because in GIT drug diffusion and drug absorption varies. Thus dual release tablet is proposed technology to overcome these difficulties [7]. In the 21st century GMP, FDA (Food and Drug Administration in 2003) initiated quality by design (QbD) and process analytical technology (PAT) principles: the purpose to build the quality in the product from beginning to the finished product [8]. Quality of a dosage form is the prime importance of a regulatory body [8].

Since its introduction by FDA in pharmaceuticals, it becomes an important paradigm of pharmaceutical formulation. The goal of QbD is to improve the quality of pharmaceutical products for patient compliance and safety. The International Conference of Harmonization (ICH) defines QbD as a systemic approach to drug development that begins with predefined objectives and uses science and risk management approaches to gain product or process understanding and ultimately process control [9]. The ICH guideline covers the various aspects of quality by design. Three ICH guidelines cover the different aspects of QbD, *i.e.,* Q8 Pharmaceutical Development, ICH Q9 Pharmaceutical Risk Management ICH Q10 Pharmaceutical Quality. The significant elements of QbD include defining the objective, *i.e.,* Quality Target Product Profile (QTTP), Determination of Critical Quality Attributes (CQAs), risk assessment, development of experimental design, implementation of controlled strategy, and continuous improvement [10].

The present review article is focused on summarizing the application of QbD for the development of dual-release bilayer tablets. A brief summary of QbD in pharmaceutical development is included to illustrate the themes and overall current status of QbD in the industry.

Chronotherapeutics: In order to understand the concept of chronopharmaceutics it is necessary to understand the concept of chronobiology and pharmaceutics. The study of biological rhythm and its mechanism of action is called as chronobiology. Biological rhythm can be defined as a number of characters. Franz Halberg was the first who coined the term circadian from latin circa means about and dies, meaning day. Oscillations having a shorter duration of action are called as ultradian. (One cycle in less than 24 h). Oscillation having a longer duration of action is called as infradian. (One cycle in more than 24 h). Pharmaceutics is the area that deals with the design and evaluation of dosage forms to assure quality, safety, accuracy, and reliability. Chronopharmaceutics is the branch of pharmaceutics that deals with the design and evaluation of drug delivery systems that release bioactive agents at the rhythm that ideally matches the biological requirement of given disease therapy. It is usually considered a time-controlled and site-specific drug delivery system [1]. Most of our body's internal functions are cylindrical. These are regular routines like walking and sleeping, a monthly pattern like women's menstrual cycle, and seasonally routine like seasonal affective disorders during winter months. The role of the human body's biological rhythm, also called biological clocks, in the quarrel of disease, has come under study [11].

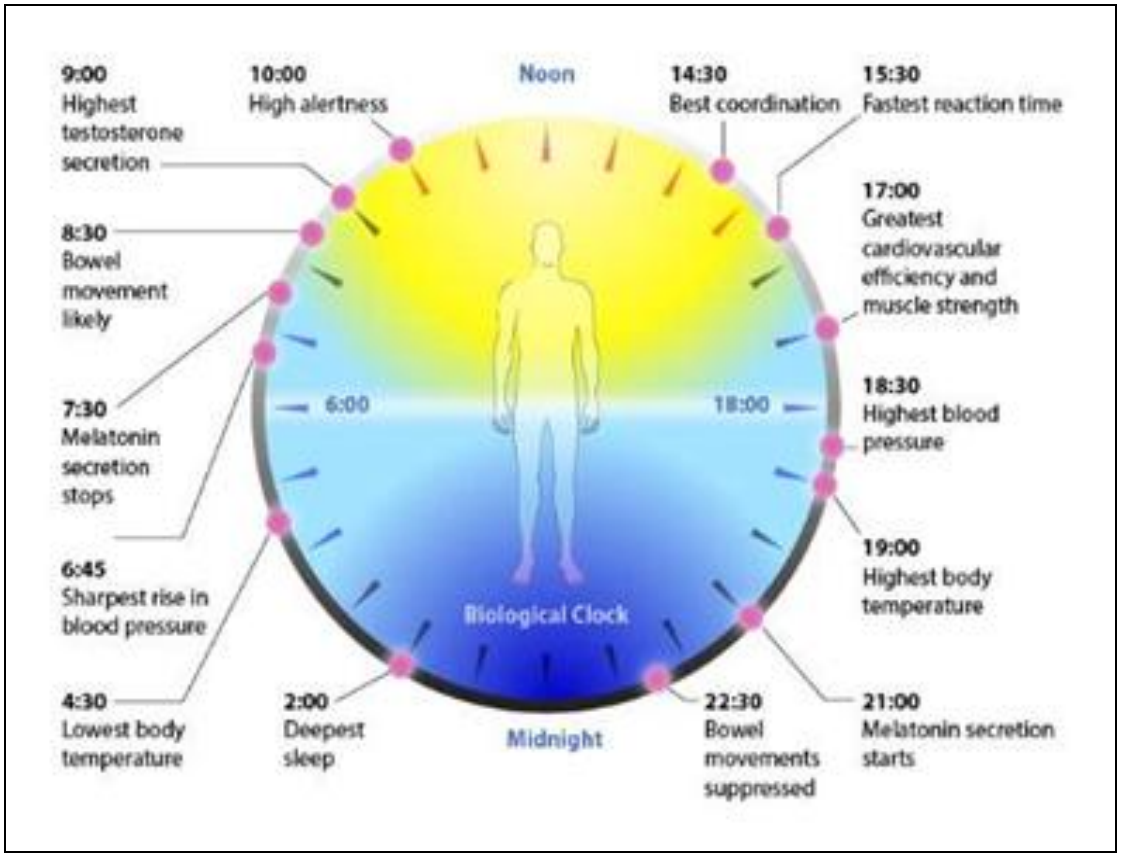


FIG. 1: HUMAN BODY CIRCADIAN RHYTHM

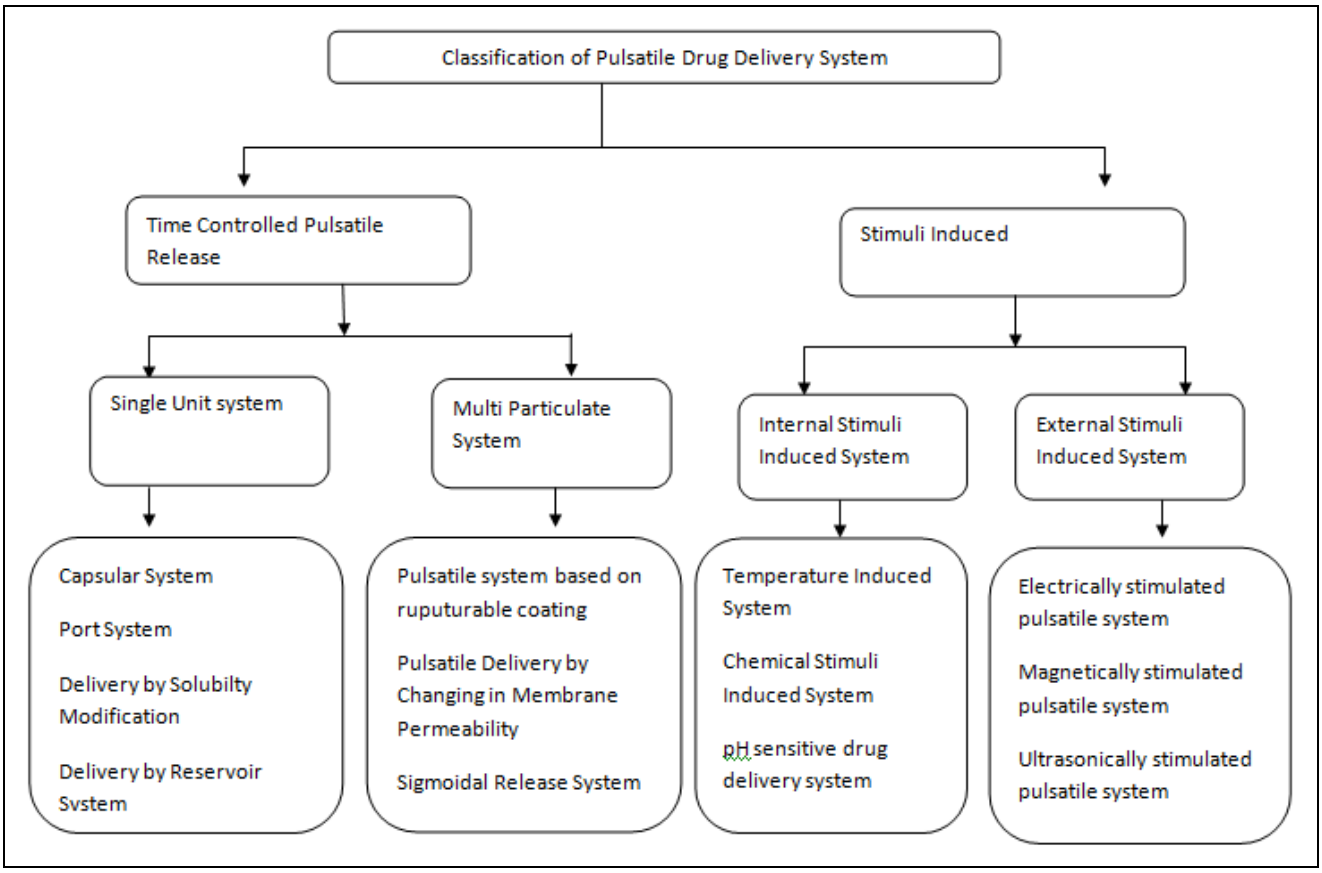
Ideal Characteristics of Chronotherapeutic Drug Delivery System: [11]

1. Rapidly working and drug delivery at a high symptomatic rate.
2. Like various treatment is also has start, middle and end, to it is easy to predict at what time it will show pharmacological action.
3. Patient compliance can be easily achieved.

Disadvantages: [11]

1. Unknown degree of risk.
2. Chemotherapy is supposed to be less productive than as usual.
3. Adjustment is required till patient's next comfortable schedule

Classification of Pulsatile Drug Delivery System: [12]



Need for Chronotherapeutic Drug Delivery System: [12] Various numbers of diseases shows pathognomonic following biological rhythm:

1. Asthma: Circadian changes are observed in normal lung function during early morning hours. The diminished lung function is mostly pronounced in people with asthma. It is usually highest at 4 am and lowest at 4 pm when asthma is more prevalent.

2. Arthritis: Patient with rheumatioid arthritis have more pain from midnight to early morning while it is less during day. For all form of arthritis chromotherapy using NSAID should be timed out to ensure the highest blood level concide with peak pain.

3. Duodenal Ulcer: At midnight, gastric acid secretion is high. Nocturnal acid suppression is an important factor in duodenal ulcer healing, a once-daily bedtime dosage regimen is recommended for H2 antagonist.

4. Diabetes: By studying the circadian behavior in blood and glucose secretion diabetes was studied. It was found increased post cibbos.

5. Neurological Disorders: Chronological rhythm of epilepsy and convulsion was investigated. It is found that brain area with highest concentration of noradrenergic nerve terminals and non adrenaline have circadian rhythm in their content of noradrenaline.

6. Cardiovascular Diseases: During morning hours most frequently occurring diseases are angina pectoris, acute myocardial infarction, sudden cardiac death, stroke, *etc*. Cardiovascular events were found active from 6 am to noon.

Need of Bilayer Tablet: [6]

1. Delivery rate of single or two different API's can be controlled.
2. By sand witching with one or two inactive layers total surface area available for API layer can be altered in order to obtain sellable or erodible barrier for modified release.
3. Incompatible APIs can be separated from each other, and the release of API from a single layer can be controlled.

Advantages: [6, 7, 8]

1. Cost-effective as compared to other dosage forms.
2. Chemical and microbial stability is more.
3. Packaging and shipment is easy
4. Identification is simple.
5. By applying the coating technique, objectionable odor and bitter taste can be masked.
6. Acceptable and suitable for large-scale production.
7. When swallow, there is the least tendency of hang up.

Disadvantages: [8]

1. Weight control of the individual layer is not accurate.
2. Children and unconscious patients cannot swallow easily.
3. Bilayer tablet press is costly.
4. Some drugs having amorphous nature and low-density characteristics resist compression into dense characteristics.

Types of Bilayer Tablet: Bilayer tablet may be same (homogeneous) or different (heterogeneous) [6].

Homogeneous Type: Bilayer tablet is used when the release profile of drugs are different from each other. Bilayer tablet is prepared with one layer containing immediate release and a second layer containing extended-release dosage form.

Heterogenous Type: Bilayer tablet in which two incompatible substances are separated and is suitable for sequential release of two drugs in combination.

FIG. 2: DUAL RELEASE TABLET REPRESENTATION

General Properties of Dual Release Tablet Dosage Form: [6]

1. Must retain physical and chemical stability.
2. Bilayer tablet is supposed to release the drug in suitable and expectable manner.
3. Must retain sufficient strength to withstand mechanical shock during production, packaging, shipping and dispensing.
4. It should have chemical stability and shelf life so that there should be no alteration of medicinal agents.

Various Techniques for Bilayer Tablet:

DUREDAS: [8] Duredas or Dual Release Drug Absorption System (Elan Corporation) employs bilayer tableting technology, which is usually developed to provide two different release profiles or combined release of drug from a single dosage form. Two separate compression steps are used to prepare the tablet that combines immediate release granules (for quick onset of action) and a controlled release hydrophilic matrix within one tablet. GI tract allows the controlled release matrix to slowly absorb the fluid, which leads the matrix to expand and transforms the hydrophilic polymers into porous, viscous gels that serve as a barrier between the drug and the surrounding fluid. As the gel continuous to become larger or increase in size, fluid continuous to penetrate into the dosage form, which dissolves the drug and allows the solution to diffuse out into the controlled release.

Benefits of DUREDAS technology are:

- Two drug components have tailored release rates.
- Unit dosage form tablet presentation.
- Capable for immediate release and modified release.

Oros Push-Pull Technology: [7] Two or three layers are present in this system in which one or more layer contains the drug, and the other layer consists of the push layer. The drug layer contains drugs with two or more different agents. Thus the drug layer contains a drug that is in poorly aqueous soluble form. Further suspending agents and osmotic agents are added in this. The Tablet core is surrounded by a semi-permeable membrane.

L-OROS^{tm} Technology: [8] Use of this technology is for solubility issues. The L-OROS system is developed by Alza. A lipid gel product containing drug in a dissolved state is manufactured and coated with a barrier membrane, then osmotic push

layer, and then semipermeable membrane drilled with an exit orifice.

EN SO TROL Technology: [7] Shire Laboratories use an integrated approach for enhancing solubility of an order of magnitude or to create optimized dosage form to deliver the drug focusing on identification and incorporation of identified enhancer into controlled release technologies.

Geometrix Technology: [8] Geometrix system includes a multilayer tablet in which matrix core containing active ingredients and one or more than one modulating layer that is barriers are applied to core in the tableting process.

The objective of these barriers is to hold up the interaction of the core with the dissolution medium. To meet the vast range of therapeutic objective, eight geometric technologies are designed: Zero-order release provides a constant release rate over a specific period of time, a binary release which is used for providing the controlled release of two drugs in a single tablet; a slow quick release which provides initially constant rate of drug release followed by a quick brusting of drug release at a predetermined time, positioned release in which drug is delivered at a predetermined position in the digestive system before it starts to release active drug compound; constantly accelerating rate of drug release is provided by accelerated release; delayed-release in which predetermined lag time is provided before it starts releasing the drug molecule; in multiple pulses an initial burst of drug release is provided followed by a predetermined period of no release. Dilthiazim hydrochloride, nefidipine and diclofenac sodium are the drugs which are provided by this technology.

GEMINEX[8]: It is a dual drug delivery technology that delivers one or more drugs at different times. The release rate of two drugs can be controlled by geminex technology to enhance the individual therapeutic effect and minimize the side effects.

The pharmaceutical industry and patient has the advantage of geminex is that delivery of two different active or the same active is possible at a different rate in a single tablet. Penwest actively employs this technology in various therapeutic or pharmacological areas such as cardiovascular disorder, diabetes, and CNS disorders.

PRODAS or Programmable Oral Drug Absorption System: [8] It is a microgranules or multiparticulate drug delivery system in which controlled release minitablets having the size range of 1.5 to 4mm in diameter are encapsulated. It is a combination of multiparticulate and hydrophilic tablet technologies, thus providing the advantage of both drug delivery in a single dosage form. The desired release rate can also be obtained by combining and incorporating the minitablets into an individual dosage form. Immediate release, delayed-release, or controlled-release formulations are included in this combination. By absorption, through GI tract, this technique also enables targeted drug delivery at a specific site.

Erodible Molded Multilayer Tablet: [7] It is an erosion-based platform. The advantage of this technology is that it can deliver zero-order or delayed-release with minimal impact from gastrointestinal conditions. The technique used for preparing Egalet Erodible Multilayer Tablet is injection molding eaglet technology in which coat and matrix is present. The gradual erosion of the matrix part is used to control the drug release. Designing and Engineering of mode and release rate is by changing the matrix coat and delivering the geometry to obtain a zero-order or delayed-release. Dispersion of drug in matrix follows zero-order. The coat is able to decay naturally, but because of poor water permeability, it prevents penetration.

As the matrix comes in contact with water, it tends to erode. The erosion in the matrix is because of gastrointestinal fluid, and thus the gut movement is promoted in the GI tract. By erosion, there is complete mediation because of drug release. This technology is preferred for drugs that have physical and stability problems when they come in contact with water. To ensure accuracy, reproducibility, and low production cost this technology was developed on the basis of standard plastic injection molding.

Various Approaches Used in Bilayer Tablet: [8]

a) Floating Drug Delivery System: This is required for low density, and therefore when administered, it floats on gastric contents until the system disintegrates or the device absorb the fluid at a point at which density is such that it loses

buoyancy and thus passes more radialy from the stomach with the wave motility responsible for gastric emptying.

In this technique, a bilayer tablet is designed such that immediate dosing of the drug produces faster onset of action, and the other layer is designed in such a way that it floats on the stomach.

b) Polymeric Bioadhesive System: These are designed in such a way that the outer layer becomes fluid or tachy material that adheres gastric mucus layer or mucosa imbibe, thus imbibed during fluid flowing administration. In this gastric retention must be encouraged until adhesive forces are weakened. They are prepared with one layer containing immediate dose and another layer containing bioadhesive property.

c) Swelling System: These are designed into a small size so as not to make ingestion of dosage form difficult. When administered, they swell and disintegrate the size that precludes the passage with pylorus until drug release has progressed to the required degree.

Quality by Design (QbD) Approach for Formulation Development: QbD strategy is based on International conference of harmonization guidelines. Quality by design includes various aspects as pharmaceutical development, manufacturing process, process control, product specification, and control strategy. In quality by design approach, product specification is generally based on desired product performance and in general, quality control strategy i.e, risk-based controlled strategy. Complete QbD begins with target product profile which pharmaceutical formulators may use regarding their clinical safety and efficacy [13].

QbD Principles: [9] Systemic approaches can be accentuated by using principles of QbD in drug development which starts with predefined objectives and applying scientific understanding and risk management approaches. For implementation and understanding of QbD, two key concepts are basically introduced. The first concept is "design space." ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality." Understanding the design space for a pharmaceutical process refers to identify critical attributes for the input materials, the process, and the final product. A modified definition of design space has been proposed for analytical methods, wherein the design space includes any combination of the input variables to a method that has been demonstrated to provide assurance of the quality of the data produced by the method. Under this definition, changes within the design space of the method are not considered to be a change to the method. Another important QbD concept is that of the "control strategy." The control strategy's purpose is to ensure the final quality of the product. The control strategy is obtained from the process understanding gained from modeling the design space. For example, QbD control strategies have presented for control of the levels of chemical impurities from a synthetic process. An analytical adaptation of control strategy has been proposed, where it is defined as the controls on input factors to a method that ensures the method meets both traditional system suitability criteria and wider performance-related goals.

Elements of Quality by Design: [14] The most widely accepted elements as QbD are: [14]

Quality Target Product Profile (QTTP): Generally includes dosage form, delivery system, dose strength, *etc*. It is a predefined summary of quality characteristics of a drug product to be achieved.

Critical Quality Attributes (CQAs): Includes physical, chemical, biological, and microbiological properties or characteristics of output material, including finished drug product. Potential drug product CQAs derived from the QTPP and/or prior knowledge are used to guide the product and process development, and they should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Material Attributes (CMAs): Includes physical, chemical, biological, or microbiological properties or characteristics of input material. CMAs should lies within an appropriate limit, range, and distribution for ensuring the desired quality of that drug substance, excipients or in-process material.

Critical Process Parameters (CPPs): Parameters monitored before or in a process that influences the appearance, impurity, and yield of the final product significantly.

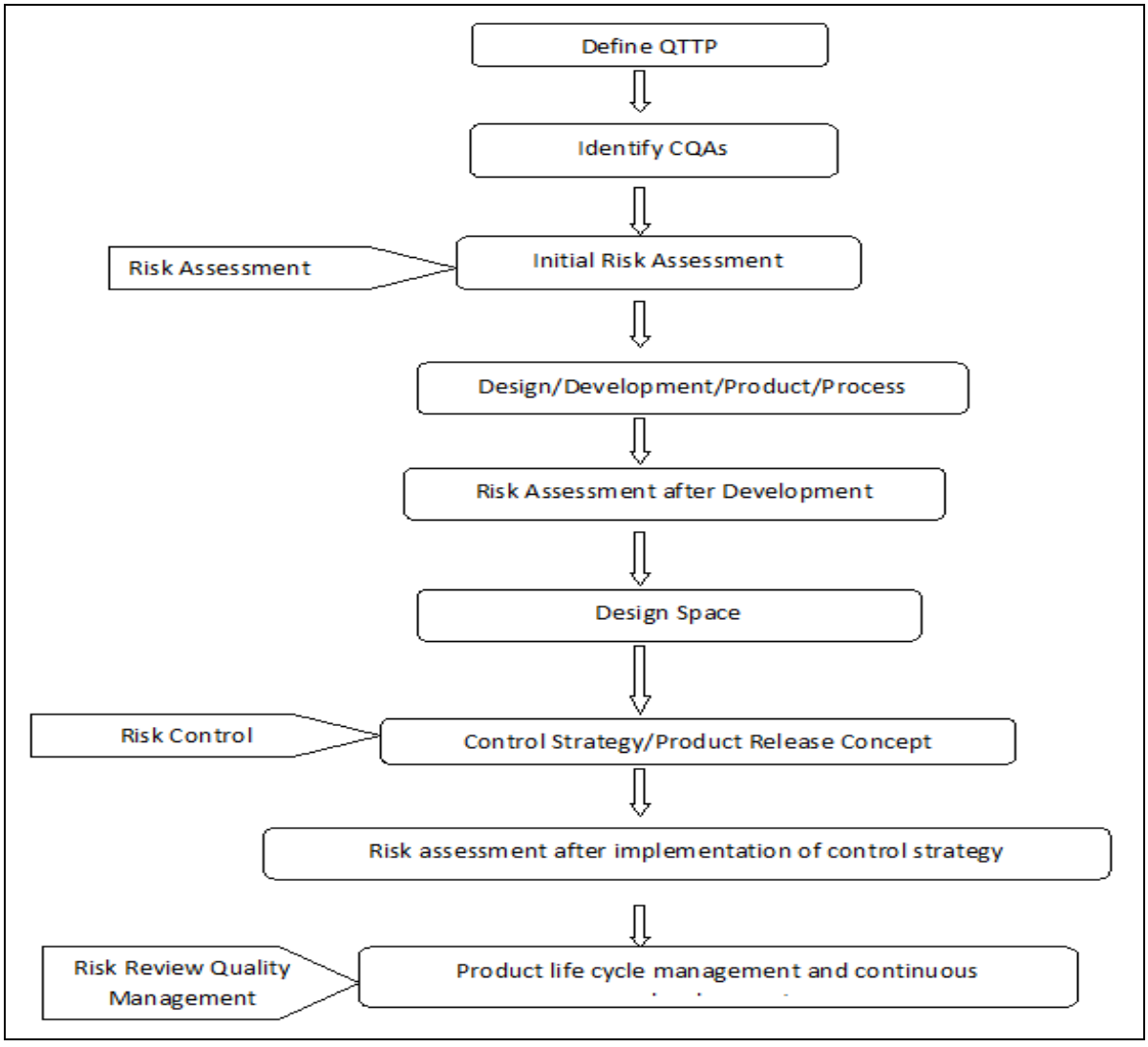
Steps for Pharmaceutical QbD Implementation: A general rule of practical implementation of QbD for the development of novel pharmaceutical product undergoes the following steps:

- Define the desired performance of the product and identify the QTPs.
- Identification of CQAs.
- Identification of possible CMAs and CPPs.
- Setup and execution of DoE to link CMAs and CPPs to CQAs and get enough information of how these parameters impact QTPP. Thereafter, a process Design Space should be defined, leading to an end product with desired QTPP
- Identify and control the sources of variability from the raw materials and the manufacturing process
- Continually monitor and improve the manufacturing process to assure consistent product quality.

Tools of QbD: [14]

- Risk Assessment
- Design of Experiment (DoE)
- PAT as an important tool of QbD

QbD Risk Management and Quality Management in Formulation Development: [15]



Interrelationship among Knowledge Design and Control Space: [5]

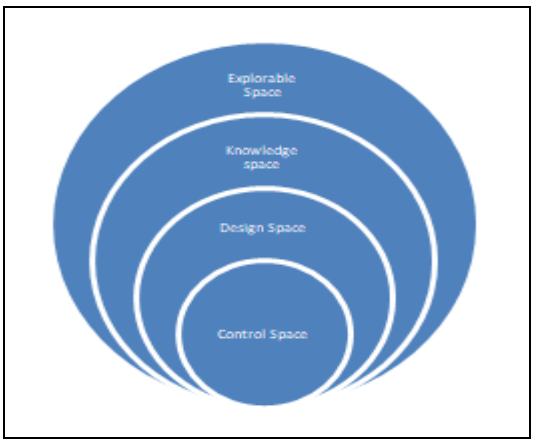


FIG. 3: KNOWLEDGE DESIGN AND CONTROL SPACE INTERRELATIONSHIP FOR QbD APPROACH

Experimental Design Used during QbD/FbD formulation in ODDS: Out of various experimental designs, the most commonly used design to optimize the ODDS are factorial, central composite design and fractional factorial design [5].

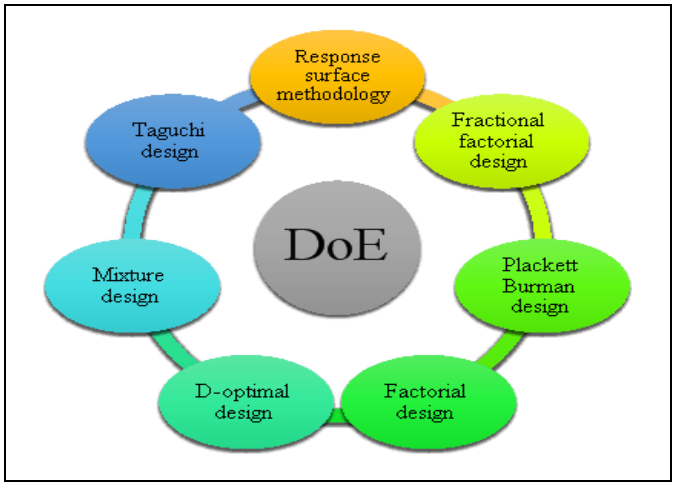


FIG. 4: CLASSIFICATION OF DESIGN OF EXPERIMENT (DoE) FOR QbD TECHNIQUE

Selection of Experimental Design: [5] Apart from various choice of design is based on amount of resources available and degree of control over making working design. For the simpler screening of various experimental parameters low resolution designs are sufficient as FFDs, Plackett- Burman Design (PBDs), or Taguchi design. Screening design can be used only for linear responses. In brief various major aspects that can be considered for experiemental design are:

1. All designs may be used for optimization rather than FMD and EVD.
2. All designs from 2^k FD, x^k FD, FFD, PBD or TgD can be used for optimization and screening studies.
3. During the determination of main effects, except PBD all 2- level designs can be used. However, for a higher number of factors greater than 6, screening must be used using FFD, PBD, Tiguchi Diagram.

Evaluation of Bilayer Tablets: [6, 7, 20]

General Appearance: General appearance of a tablet is a visual identity. It deals with tablet shape, size, color, presence or absence of odour, surface texture, physical flaw, consistency, and identifying marking.

Thickness and Size: To obtain the uniform tablet size, thickness and size are important. Thickness is determined by using vernnier caliper or screw gauze. Not uniformity in size leads to altered dose strength and can cause a problem in uniform packaging.

Tablet Hardness: The resistance of breakage during shipping or transport depends upon hardness. The various hardness tester used to measure hardness is Monsanto Hardness Tester, Pfizer Hardness Tester, Eureka Hardness Tester, Strong, and Coob's Hardness Tester, Schiwinger Hardness Tester. The limit of hardness is not more than 5 kg/cm^2.

Friability: Friability is used to measure the tablet strength so that tablet does not break during storage. For friability testing instrument Roche Friabilator is used. Tablet equivalent to weight 6.5 gm is taken and kept in friabilator. Friabilator rotates for 4 minutes at the revolution of 25 rpm, and the tablet drops from a distance of 6 inch (12 – 14 cm). Tablet are again weighed, and percent friability is calculated as

% Friability = Initial Weight – Final Weight / Initial Weight × 100

Limit: Not more than 1%n deviation in weight or 0.5-1%.

Uniformity of Weight: 20 tablets are weighed random, and the average weight is calculated, and it is compared with IP and USP limits.

TABLE 1: WORLDWIDE PATENTS ON BILAYER TABLETS

Publication Number	Drug/s	Publication date/Status	Inventors	Invention Title	Advantage
CN107432869A	Metformin hydrochloride and Englitazone	27-05-2016/ Application	Hui *et al.,*	Bilayer tablet comprising metformin hydrochloride and its preparation method with englitazone	Simple preparation process, cheaper, uniform drug content, enhanced product stability [16]
CN10682212A	Tellmisartan and Amlodipine	23-01-2017/ Applicaion	Xin *et al.,*	Method for preparing telmisartan and amlodipine double-layer tablets	Better dissolution behavior and higher stability [17]
US10016368B2	Acetaminophen and Promethazine	01-11-2016/ Application	Paul *et al.,*	Method of preparation of acetaminophen and promethazine double layer tablet.	To reduce the pain along with reduce the associated adverse effects [18]
US201202095A1	Aceraminophen and Hydrocodone Bitartarate	15-08-2013/ Application	Cruz *et al.,*	Method of Preparation of IR hydrocodone Bitartarate and SR Acetaminophen	To reduce pain over prolong period of time [19]

TABLE 2: LIMITS OF WEIGHT VARIATION TEST ACCORDING TO IP AND USP

Deviation allowed (%)	Tablet weight (IP)	Tablet Weight (USP)
10	Less than 80 mg	Less than 130mg
7.5	80 – 250mg	130mg-324 mg
5	>250mg	>324mg

Dissolution Studies: *In-vitro* dissolution study is carried out in simulated gastric fluid or simulated intestinal fluid to assess the ability to provide the controlled release. Dissolution study is carried out in USP dissolution test apparatus at 37 ℃ temperature at specific RPM or as mentioned in the monograph.

Drug Content and Release: In order to evaluate the potential for efficacy, it is important to monitor the amount of drug per tablet and batch to batch, and a measure of tablet ability to release the drug needs to be ascertained.

CONCLUSION: The review demonstrates the importance of chronotherapeutics in the drug delivery system. Knowing the circadian behavior desired dose-response can be achieved to deliver the drug in a right site, at right time, and in the right amount. Further, the review also demonstrates the importance of dual release tablet in the formulation of chronotherapeutic drug delivery system. A brief focus on gout or arthritis chronomodulated formulation was given. The various techniques used for the formulation of dual-release tablets are discussed in brief. Optimize means to make as effective as much as possible. So the optimization is discussed in brief to make the optimized chronomodulated dual-release formulation. Various patented dual release tablets are discussed in brief, and evaluation parameters for dual release tablets were also discussed. In brief, the review article is focused on how to formulate optimized dual release formulation for chronomodulated drug delivery system.

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CONFLICTS OF INTEREST: The author doesn't have any conflict of interest.

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