1. Introduction

1.1 Disease prolusion
Migraine is defined by its clinical phenomenology. There is no diagnostic test or biological marker to confirm migraine. This ambiguity clearly hinders the development of therapeutic agents to treat or prevent this disease. Migraine is a very common neurobiological disorder that is caused by the increased excitability of the central nervous system. It is a primary episodic headache disorder characterized by various combinations of neurological, gastrointestinal and autonomic changes.

Migraine is a cabalistic disorder characterized mainly by pulsating headache, usually restricted to one side, which comes in attacks last 4-48 hrs and may or may not be associated with nausea, vomiting, sensitivity to light and sound, flashes of light, vertigo, loose motions and other symptoms. Two major types are-

- Migraine with aura (classical migraine) in which headache is preceded by visual or other neurological symptoms
- Migraine without aura (common migraine)

In moderate migraine throbbing headache is more intense, persistent for 6-24 hrs, associated with nausea, vomiting and other features are more prominent and the patient is functionally impaired. Severe migraine patients suffer 2-3 or more attacks per month of severe pulsating headache which last 12-48 hrs, along with vertigo, vomiting and other symptoms. The subject is incapacitated during the severe migraine attack.

1.1.1 Characteristics of migraine
The migraine attack consists of the following phases:

1.1.1.1 Premonitory phase
Symptoms occurs hrs to days before the onset of headache. The most common symptoms are feeling weary and tired, difficulty in concentrating and stiff neck. Poor functioning commonly predicts headache.
1.1.1.2 Aura phase
The migraine aura consists of focal neurological symptoms that precede, accompany, or (rarely) follow an attack. Aura usually develops over 5 to 20 mins, lasts for less than 60 mins. It can be visual, sensory, or motor, and can involve language or brain stem disturbances.

1.1.1.3 Headache phase
The typical headache is unilateral, gradual onset, throbbing, moderate to mark in severity and aggravated by movement. Pain lasts for about 4 to 72 hrs in adults and one to 72 hrs in children. Anorexia is very common. Nausea occurs in almost 90% of the patients while vomiting occurs in about one third patients.

1.1.1.4 Resolution phase
Tired, irritable, listless, scalp tenderness, mood changes are commonly observed features in the resolution phase. The general somatic symptoms accompanying migraine, in the order of frequency are sensitivity to light, blurred vision, nausea, tenderness about the scalp, dizziness or lightheadedness, lethargy, vomiting, retention of fluid, photopia, vertigo, anxiety, parenthesis, diarrhea, fortification spectra, nasal stuffiness, mild aphasia, syncope or near syncope, severe confusion, seizures, fever, hemi paresis or hemiplegia, ataxia and/or dysarthria (brain stem dysfunction).

1.1.2 Treatment for migraine
Currently migraine therapy is ranging from non specific to specific therapy. Drugs including paracetamol, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, caffeine, isometheptene, butalbital, codeine and / or opiates alone or in combination are categorized under non specific therapy.

Specific therapeutical agent includes ergotamine, dihydroergotamine mesylate and the triptans for migraine treatment. A new class of acute migraine specific medications, the triptans, was developed in 1980’s. The acute abortive treatment of migraine was revolutionized by the highly selective 5-HT receptor agonist. Triptan relieved the headache and associated symptoms but did not normalize the altered cortical blood flow in the brain stem.
Triptans administered early prevented central sensitization. Late triptan intervention did not reverse central sensitization. Trigeminal sensitization during migraine attacks leads to development of cutaneous allodynia. Triptans can prevent but not reverse cutaneous allodynia. Without allodynia, triptans completely relieved the headache and blocked development of allodynia. In 90% of the attacks, with established allodynia, triptans provided little or no headache relief and did not suppress allodynia. However, late triptan therapy eliminated peripheral sensitization (throbbing pain aggravated by movement) even when pain relief was incomplete and allodynia was not suppressed.

Patients with episodic migraine are advised to administer their acute medication as soon as possible after the recognition of their characteristic migraine headache, preferably within 20 mins, before pain become moderate or severe.

Acute therapy with triptans is significantly more effective, when pain is mild. Early administration of triptans has been shown to improve a wide range of headache response outcome.
1.2 Therapy prolusion

Drug formulations administrated by several routes but, oral drug delivery system is the most preferable route due to the safety, ease of administration, economical, self medication and patient compliance. The solid oral dosage forms are usually available in various formulations such as tablets, capsules, and powders. Oral drug delivery formulation mostly prepared as conventional type and sometimes modified release in the form of immediate release. Conventional release drug therapy has some limitations such as:

- Little or no control over the release of the drug and effective concentration at the target site
- The dosing pattern results into constantly changing unpredictable plasma concentrations, leading to marked side effects
- Not suitable for the drugs which can cause irritation to gastric mucosa
- Bioavailability of the drug may vary depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal tract, gastrointestinal motility, etc.

Immediate release drug therapy also has certain limitations such as:

- Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance
- Fluctuations in the drug concentration may leads to under medication or over medication as the Css fall or rise outside the therapeutic range.
- The fluctuating drug level may results into adverse effects especially drug having small therapeutic index

To achieve desired therapeutic effect and to overcome the problem of conventional and immediate release the another type of modified drug delivery system such as a sustained, extended or controlled release drug delivery system is developed, so that solid oral dosage forms are proved to be more useful as compared to other dosage form. It has several advantages over traditional systems such as:

- Improved efficiency
• Reduce toxicity
• Improved patient compliance
• Improved bioavailability of drug
• Reduce chances of dose dumping
• Provide plurality of drug release
• Reduce dosing frequency

1.2.1 Modified drug delivery systems
Modified dosage forms are designed to release the drug over a given period of time or after the drug formulation reaches to the site of action.

Classification: Modified release dosage forms are classified\(^6\) as follow-

- Extended release
  - Sustained release
  - Controlled release
- Delayed release
- Site-specific targeting
- Receptor targeting

1.2.1.1 Extended release
Oral DDS release the drug over prolonged period of time. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release preparation can be formulated by using sustained or controlled release formulation approach\(^7\).

- **Sustained release dosage forms** are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. The onset of action is delayed and therapeutic effect is sustained. Sustained release systems generally imitate zero order release by providing drug in a first order manner\(^8\).

- **Controlled release dosage forms** is referring to the delivery of formulation in response to stimuli or time, generally achieved by obtaining “zero order” release from the dosage form which is independent of the amount of drug.\(^7\)
1.2.1.2 Delayed release
Delivered release systems are those that use repetitive, intermittent dosing of a drug, from one or more immediate-release units incorporated into a single dosage form. E.g. repeat-action tablets and capsules, enteric coated tablets where the time release is achieved by a barrier coating^3^.

1.2.1.3 Site-specific targeting
Site-specific drug delivery refers to delivery of a drug directly to a certain biological location. In case of site-specific release, the target is situated nearby or on the diseased organ or tissues.

1.2.1.4 Receptor targeting
For receptor release, the particular receptor is targeted for a drug within an organ or tissue. Both of these systems satisfy the special aspect of drug delivery and are also considered to be controlled drug-delivery system^9^,^7^.

1.3 Sustained release drug delivery system
During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new drug delivery systems, amongst those the controlled / sustained release dosage forms admired by physician as well patient. The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule’s inherent kinetic properties. Thus, optimal design of a sustained/ controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs^7^,^10^.

Sustained release drug administration means not only the prolongation of duration of drug delivery similarly to the action in the sustained and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. The controlled release of drug substances and their effective transport to the sites of action
can be exploited to maximize the beneficial clinical response and to minimize incidence of unbeneﬁcial adverse reactions and side effects\textsuperscript{11}.

**Advantages**
- Decreased local and systemic side effects
- Reduces gastrointestinal irritation
- Better drug utilization, reduction in total amount of drug used
- Improved efficiency in treatment, optimized therapy, more uniform blood concentration
- Reduce ﬂuctuation in drug level and hence more uniform pharmacological response
- Increase in drug activity with chronic use
- Improve bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release
- Improved patient compliance, less frequent dosing, reduced night-time dosing, reduced patient care time
- The importance of patient compliance in successful drug therapy is well recognized. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate

**Disadvantages**
- Dose dumping
- Less ﬂexibility in accurate dose adjustment
- Poor IVIVC
- Increased potential for ﬁrst pass clearance
- Drug with single dose exceeding 1 gm, diﬃcult to formulate
- Costly

### 1.3.1 Classification of oral sustained/controlled release system

#### 1.3.1.1 Diffusion controlled Systems\textsuperscript{12}

1.3.1.1.1 Reservoir devices

A core of drug (reservoir) surrounded by a polymeric membrane characterizes them.
The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are -

- Zero order drug release
- The release rate is polymer type dependent
- High molecular weight compounds are difficult to deliver through the device

1.3.1.2 Matrix devices ¹³
It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are-

- Zero order release can’t be obtained
- Easy to produce than reservoir devices
- High molecular weight compounds are delivered through the device

1.3.1.3 Dissolution controlled systems ¹⁴

1.3.1.3.1 Matrix dissolution controlled systems
Aqueous dispersions, congealing, spherical agglomeration.

1.3.1.3.2 Encapsulation dissolution controlled systems
Particles, seeds, granules can be coated by microencapsulation technique.

1.3.1.4 Diffusion and dissolution controlled systems
In a bio-erodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

1.3.1.4.1 Matrix tablets
These are the type of controlled drug delivery systems in which the drug is released in continuous manner by both dissolution and diffusion controlled mechanisms. To control the release of the drugs having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials ¹⁵.

One of the simplified approach to manufacture of sustained release dosage forms is the direct compression of drug, release retardant, and additives to form a tablet. Alternatively drug retardant blend may be granulated prior to compression, such tablets
are called as matrix tablets.

**Advantages**
- Easy to manufacture
- Versatile, effective and low cost

**Disadvantages**
- The remaining matrix must be removed after the drug has been released
- The drug release rates vary with the square root of time
- Release rate continuously diminishes due to an increase in diffusion resistance and/or a decrease in effective area at the diffusion front

**1.3.1.5 Matrix devices materials**

<table>
<thead>
<tr>
<th>Table 1: Matrix carrier system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A). Hydrophobic carriers:</strong></td>
</tr>
<tr>
<td>✭ Insoluble inert matrix carrier - Polyethylene, Polyvinyl Chloride, Methyl Acrylate-Methacrylate Copolymer, Ethyl Cellulose, Etc.</td>
</tr>
<tr>
<td>✭ Insoluble erodible matrix Poly Vinyl Alcohol, Stearic Acid, Polyethylene Glycol, Polyethylene Glycol Monostearate, Triglycerides</td>
</tr>
<tr>
<td>✭ Digestible base (fatty compounds) Glycerides – Glyceryl tristearate, Fatty Alcohols, Fatty Acids, Carnauba Wax</td>
</tr>
<tr>
<td>✭ Nondigestible base (insoluble plastics) Methylacrylate -Methylmethacrylate, Polyvinyl Chloride, Polyethylene, Ethyl Cellulose</td>
</tr>
</tbody>
</table>

| **B). Hydrophilic polymers:** Methyl Cellulose, Sodium Carboxy Methyl Cellulose, Hydroxy propyl Methyl Cellulose, Sodium Alginate, Xanthan Gum, Polyethylene Oxide, Carbopolst |
1.4 Hot melt agglomeration

Melt agglomeration is a process in which the solid fine particles are bound together with the help of molten binding liquid by agitation, kneading, and layering process to form agglomerates. Melt agglomerates are prepared by melt pelletization and melt granulation technique. Dry agglomerates are obtained as the molten binding liquid solidifies by cooling.

During the agglomeration process, the meltable binder may be added as molten liquid, or as dry powder or flakes, resulting in change in the size and shape of the agglomerates. Typically, the melting points of meltable binders ranges from 50 to 80°C. A binder having lower melting point cannot be used where melting or softening of the binder occurs during handling and storage of agglomerates. The formation of melt agglomeration process is similar to that of wet agglomeration process.

![Figure 1: Modes of melt agglomeration](image)

Melt agglomeration is based on the mechanism of distribution and immersion in which distribution of molten binding liquid on the surfaces of primary particles will occur and agglomerates are formed via coalescence between the wetted nuclei as shown in Figure 1, whereas in an immersion mode, nuclei formed by immersion of the primary particles onto a surface of droplet of molten binding liquid [Figure 1].

The distribution of molten binding liquid to surfaces of nuclei has to be effected by densification prior to coalescence between the nuclei. Depending on the relative size between the solid particles and the molten binding liquid droplets, the distribution will be a dominant mode when the molten binding liquid droplets are smaller than the solid
particles or of a similar size. The distribution mode is promoted by a low molten binding liquid viscosity on the other hand; the immersion mode will dominate when the molten binding liquid droplets are larger than the solid particles. In the case of immersion it is more favorable for molten binding liquid of high viscosity, which could resist breakup by dispersive forces.

**Advantages**

- Neither solvent nor water is used
- Time consuming drying steps are eliminated
- There are no requirements on the compressibility of active ingredients
- The procedure is simple, continuous and efficient
- Uniform dispersion of fine particle occurs
- Good stability at varying pH and moisture levels
- Safe application in humans due to their non-swellable and water insoluble nature

**Disadvantages**

- Requires high energy input in the form of heat
- Cannot be applied to heat-sensitive materials
- Meltable binder used in this technique should have analogous melting point

1.4.1 **Factors affecting melt agglomeration**

1.4.1.1 **Processing variables**

Mixing time, mixing speed, mixer load, melting temperature and method of binder addition are the different processing variables having effect on melt agglomeration process. Increase in mixing time or mixing speed promotes agglomerate growth through squeezing the molten binding liquid from agglomerate core to surfaces by means of a densification process. It leads to increase in the degree of liquid saturation of agglomerates. The deformable surfaces of agglomerates were rounded by continuous impeller rotation leads to the formation of spherical pellets.
1.4.1.2 Formulation variables

The different formulation variable includes the effects of size distribution, shape, density, and packing properties of fine solid particles. The solid particles having mean size smaller than 1 µm is usually difficult to prepare melt agglomerates because it leads to a potentially uncontrollable melt agglomerative process. Generally, particles having size range between 20 and 25 µm are preferable for the production of melt agglomerates. Excessively large solid particles, with a mean size over 100 µm, produce mechanically weak agglomerates or fines.

Particle size, size distribution, shape, and density affect the packing geometry of solid agglomerates. The strength of particulate interlocking, state of liquid distribution, and saturation of agglomerates can be altered via modification in these properties of fine solid particles.

1.4.2 Binder

The volume, rheology, surface property and particle size of binder shows significant effect on melt agglomeration process and other formulations or processing variables. The growth of melt agglomerates is promoted predominantly by an increase in viscosity and specific volume as well as a decrease in surface tension of the molten binding liquid.

The influence of viscosity and surface tension of molten binding liquid on melt agglomerates are affected by product temperature, mixing speed, and physicochemical properties of the fine solid particles. The particle size of binder shows less effect on melt agglomeration except when high-viscosity binder is used and at early agglomerative phase.

1.4.3 Techniques for melt granulation

1.4.3.1 Spray congealing

Spray congealing is a melt technique of high versatility, which can be applied to process the raw melttable materials into particles of defined size and viscosity value for the melt agglomeration process. Processing of melttable materials by spray congealing involves spraying a hot melt of wax, fatty acid, or glyceride into an air chamber below the melting point of the melttable materials or at cryogenic temperature. Spray-
congealed particles (10–3000 μm in diameter) are obtained upon cooling. The congealed particles are strong and nonporous as there is an absence of solvent evaporation. Ideally, the meltable materials should have defined melting points or narrow melting ranges. At the processing temperature viscosity modifier, either meltable or non-meltable, may be incorporated into the meltable matrix to change the consistency of the molten droplets.

### 1.4.3.2 Tumbling Melt Granulation

A newer melt agglomeration technique used for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a fluid-bed granulator. The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value. The particle size of a meltable material should be 1/6 or lower than the diameter of the seeds. High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity.

Both particle size and viscosity of the meltable materials play a significant role in the melt agglomeration process. The control of the melt agglomeration process is best initiated by using meltable materials having controlled properties. For the melt pelletization and melt granulation process, it is desirable that meltable materials have a high viscosity to improve the mechanical strength of the agglomerates, but a reduced particle size to prevent uncontrollable agglomerate growth. In tumbling melt granulation, small meltable particles with sufficient viscous binding forces are obligatory for the production of spherical beads.
1.5 Liquisolid technique

Development of sustained release oral dosage form is efficacious in terms of safety, effectiveness and patient compliance. Liquisolid technology is economical, reasonable formulation production proficiency parallel to conventional tablets and enhanced or retards the dissolution rate\(^{31}\). It reveals that liquisolid method has the prospective for the retardation of drug dissolution rate and thereby gives rise to sustained release system by using hydrophobic carriers in liquisolid system formulation\(^{32}\).

The mechanism of sustained release is owed to efficient encapsulation of drug particles by the hydrophobic polymers. The presence of non-volatile solvent reduces the glass transition temperature (Tg) of polymers and imparts flexibility\(^{32}\). Therefore, reduction of Tg of the polymer might be the another reason for the liquisolid sustained release tablets. Hence, the drug is surrounded by the polymer, lead to restricted leaching of the drug and produce sustained release formulation. The Liquisolid compacts have two major formulation components viz., powder substrate and liquid medication\(^{33}\).

The powder substrate mainly consists of-

- **Compression enhancer** - preferably large and porous carrier particles
- **Flow enhancer** - very fine, highly adsorptive coating material particles

**Advantages**

- Can be used in formulation of controlled and sustained drug delivery
- Sustained release liquisolid tablets demonstrate constant dissolution rates (Zero Order Release)
- Production of liquisolid system is analogous to that of conventional tablets formulation
- Feasibility of industrial production for pilot plant
- Drug can be molecularly dispersed in the formulation
- Sustained release of liquisolid tablet containing water soluble drug reveals constant dissolution rate

**Disadvantages**

- Only low dose drug can be formulated into the liquisolid system
- Higher amounts of carrier and coating materials are required
- Not suitable for formulation of high dose water insoluble drugs
For flow properties enhancement more powder is needed which results into increase in tablet weight and difficult to swallow

1.5.1 Classification of liquisolid systems

A Liquisolid system is classified into three sub groups based on the type of liquid medication used in formulation as follows-

- Powdered drug solution
- Powdered drug suspension
- Powdered liquid drug

The former two groups prepared by altering drug into solutions and suspensions form while the later is produced from the preparation of liquid drugs into liquisolid systems.

Based on the formulation technique used, a liquisolid system is classified into two categories.

1. Liquisolid compact
2. Liquisolid microsystem

The term “liquisolid compact” refers to immediate or sustained release tablets or capsules prepared by combining suitable adjuvant required for tabletting or encapsulation such as lubricants, carrier material and for rapid or sustained release action, such as disintegrants or binders, respectively.

Figure 2: Schematic representation of liquisolid systems
1.5.2 Formulation design

The different components were added in the formulation design of liquisolid tablet as follow-

- **Liquid medication**
  Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water soluble or insoluble drugs in suitable non-volatile solvent systems.

- **Non-volatile solvent**
  Non-volatile solvent may be hydrophilic or lipophilic in nature depending upon the type of formulation immediate or sustained release, respectively. Non volatile solvent should be inert, with high boiling point, water miscible.

- **Carriers**
  Carrier materials play the main role in obtaining the dry form of powder from the drug in liquid state. Carrier material should be a porous material possessing sufficient absorption capacity for liquids. It was observed that the specific surface area of the carrier is an important factor in the formulation of liquisolid systems. Carrier selection depends on its liquid binding capacity, flowability of powders and compressibility.

- **Coating materials**
  Coating material refers to a material possessing fine and highly adsorptive particles such as various types of silica which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.

<table>
<thead>
<tr>
<th>Component</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-volatile solvents</td>
<td>PEG 400, PEG 200, PEG 4000, , Tween80, etc.</td>
</tr>
<tr>
<td>Carriers</td>
<td>Avicel, etc.</td>
</tr>
<tr>
<td>Coating Materials</td>
<td>Aerosil, Colloidal silica, Cab-O-sil, etc.</td>
</tr>
<tr>
<td>Super Disintegrants</td>
<td>Sodium starch glycolate, Crospovidone, Sodium croscarmellose</td>
</tr>
</tbody>
</table>

Liquisolid technology is used to transform liquid material into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected
excipients i.e. carrier and coating material. The liquid part, which can be a liquid drug, a drug suspension or a drug solution in suitable nonvolatile liquid vehicles, is incorporated into the porous carrier material shown in Figure 240.

1.5.3 Liquisolid formulations for sustained drug release

The Liquisolid tablet preparation comprises a calculated amount of pure drug weighed and dissolved in the suitable amount of non-volatile solvent in a molecularly dispersed state. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally. For attaining a good flow properties, trial and error methods were used i.e. changing the carrier:coating material ratio from 50:1 to 5:1 according to new mathematical model expressions proposed by Liao, and a suitable disintegrant is added.

Finally, coating material is added which provide dry appearance to the blend and support the carrier material to achieve good compression properties. Liquid medication is incorporated into carrier material which has a porous surface and closely intertwined fibers. A large surface area and high absorptive properties of the coating material provides the specific flow properties to the liquisolid system.

1.5.3.1 Sustained drug release Mechanism from liquisolid systems

The principal mechanism involved in the sustained release liquisolid formulation is employing hydrophobic carrier instead of hydrophilic carrier which leads to poor wetting of the liquisolid compacts, eventually resulting the slow disintegration and thus prolong the drug release. XRD and DSC analysis confirmed that sustained drug release from liquisolid compacts is due to change in crystallinity and complex formation. The non volatile liquid vehicle also sustains the drug release.

In liquisolid compacts the coalescence of the polymer particles occurs at lower temperature which organizes the matrix with lower porosity and higher tortuosity and fine network of the hydrophobic polymer surrounding to drug resulting in a formulation of sustained release.
1.6 Quality by design prolusion
The pharmaceutical industry has been traditionally based on experienced and fixed procedures not only for product and process development, but even for product manufacturing. This situation has been partly because of rigid regulatory environment which strongly contributed to hinder improvements and innovation in the manufacturing technologies. The efficiency of the manufacturing processes is not only pressure source for pharmaceutical companies, but they also deal with increased costs for new drug development and results into decline in research and development productivity. Considering this technical and economic conditions, a decade ago the FDA launched the Quality by Design (QbD) project, a new approach to pharmaceutical process development and manufacturing, which favors an efficient and flexible environment to reliably produce high quality products, without extensive regulatory oversight.

According to QbD, the quality must be “built into” the product since its design, through an extensive mechanistic understanding of the relations between the product quality and the parameters that can have an impact on it.

1.6.1 Elements of quality by design
The main pharmaceutical development elements are explained as follows-

1.6.1.1 Target product profile (TPP) and quality target product profile (QTPP)
TPP covers the overall objectives of safety and efficacy of a drug development program and thus QTPP establish the product development program and process patient oriented. The primary components of TPP are mainly clinical pharmacology aspects such as indications, side effects, route of administration, dose, etc. The drug product should possess quality properties in order to meet the objectives set in TPP are summarized under target product quality profile (TPQP) which is quantitative alternate for the clinical safety and efficacy.

1.6.1.2 Critical Quality Attributes (CQA)
A critical quality attribute (CQA) is “a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality”. The identification of a
CQA from the QTPP is based on the severity of harm to a patient. CQAs for different QTPP are of following types-

All the critical quality attributes or characteristics must be within an established/specified range/limit to ensure product quality, safety and efficacy53.

1.6.1.3 Quality risk management

The components of a quality risk management process are

- Risk assessment (includes risk identification, risk analysis and risk evaluation)
- Risk control (it includes risk reduction and risk acceptance)
- Result of the quality risk management process and
- Risk review

1.6.1.3.1 Risk management tools for QbD

There are many tools and techniques used while applying QbD approach. Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are: flowcharts, check sheets, process mapping, cause and effect diagrams (also called an Ishikawa diagram or fish bone diagram)54.

Other important tools include statistical tools, process analytical technology (PAT) and various risks management tools55. The ICH Q9 guideline describes the principles of quality risk management to guide development efforts50,56.

Failure mode effect analysis includes Failure Mode Effects Analysis (FMEA)56,57, Failure Mode, Effects and Criticality Analysis (FMECA)56,58,59, Fault Tree Analysis (FTA)56, Hazard Analysis and Critical Control Points (HACCP)56,60, Hazard Operability Analysis (HAZOP)56, Preliminary Hazard Analysis (PHA)56,61 and risk ranking and filtering56,59.

1.6.1.4 Design space

The ICH Q8 guideline defines the design space as “the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. The design space is considered as the final achievement of process understanding in the development of new products and processes. However, a design space can be updated over the lifecycle of the
product as additional knowledge is gained. According to the definition, the design space has a multivariate nature, suited to explore not only the effect of the single material attributes or process parameters, but also their interactions and combined effects\textsuperscript{50}.

1.6.1.5 Control strategy and real time release testing

The control strategy is defined as “A planned set of controls, derived from current product and process understanding, which ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control”\textsuperscript{52}.

In summary, a control strategy can include, but it is not limited to, the following-

- Control of input material attributes (e.g. APIs, excipients, primary packaging materials), based on understanding their impact on process ability or product quality
- Product specification(s)
- Controls for unit operations that have an impact on product quality
- In-process or real-time release testing in lieu of end-product testing
- A monitoring program for verifying prediction models performances

1.6.1.5.1 Supporting statistical tools

Statistical tools can support and facilitate quality risk management and support QbD data submission. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. Some of the principal statistical tools commonly used in the pharmaceutical industry are control charts e.g.(acceptance control charts, control charts with arithmetic average and warning limits, cumulative sum charts, Shewhart control charts ), weighted moving average, Design of Experiments (DoE), histograms, Pareto charts, process capability analysis (PCA).

1.6.1.5.2 Experiments designs

Fisher devised experimental design principles were used, which have found applications in many areas including pharmaceutical development\textsuperscript{62}. Pharmaceutical
Introduction

Product development is designed to yield maximum knowledge of product performance systematically over a wide range of material and process attributes. Some commonly used experimental designs are shown in Table 3:

Table 3: Commonly used factorial design

<table>
<thead>
<tr>
<th>Designs</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factorial design</td>
<td>Used for screening experiments. Fractional factorial designs involve lesser experiment than full factorial design. The major benefit of using factorial design is that all estimated effects and interactions are independent of effects of other factors.</td>
</tr>
<tr>
<td>Central composite design</td>
<td>In this design each factor has five levels. Sometime referred as star design. The design permits a full second order model to be investigated. It is used for optimization purpose.</td>
</tr>
<tr>
<td>Plackett–Burman design</td>
<td>Used for screening experiment and also for robustness testing. Generally it is two level factorial design for studying (N-1) variables in N experiments where N is multiple of 4.</td>
</tr>
<tr>
<td>Box–Behnken design</td>
<td>Box–Behnken design requires an experiment number according to ( N = k^2 + k + Cp ), where ( k ) is the factor number and ( Cp ) is the replicate number of the central point. In this design each factor has three levels.</td>
</tr>
<tr>
<td>D optimal design</td>
<td>D-optimal designs used for multi-factor experiments. When there is irregular experimental region in screening, optimization and mixture design. In case of optimization designs with qualitative factors are also for special number of runs and Model upgrading</td>
</tr>
<tr>
<td>Mixture design</td>
<td>Involve experiments where the response ( Y ) is a function of the proportions of the ingredients in the mixture and not of the amounts of the ingredients. We can apply several classical mixture design approaches, such as simplex, extreme vertices, and lattice.</td>
</tr>
<tr>
<td>Taguchi technique</td>
<td>Taguchi’s methodology is used in the optimization of pharmaceutical products quality and the design of the processes in order to become insensitive to the noise sources without their elimination. Signal/noise ratio is an indicator of the performance characteristics of the pharmaceutical products/processes.</td>
</tr>
</tbody>
</table>