CHAPTER 1

INTRODUCTION
1 Introduction

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long term therapy for the treatment of chronic disease conditions like Human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), conventional formulations are required to be administered in multiple doses and therefore have several disadvantages like accumulation of drug in multi-dose therapy, poor patient compliance and high cost. Extended release formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects and increase safety margin for high potency drugs. Hence, extended release formulations are preferred for such therapy.1-5

In order to achieve therapeutic effect, a drug needs to reach the right place in the body at the right time. For some drugs, this may be achieved by simple solutions or solid dosage forms with an instant drug release while, for others, one has to modify the drug release. To understand the literature within the area of modified drug release, it is important to be aware of the standard terms used for dosage forms within this field. Malinowski and Marroum have summarized these terms in the book Encyclopedia of Controlled Drug Delivery.6 The authors state that, modified-release (MR) formulations refer to “dosage forms for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.” One group of MR formulations is the delayed-release dosage form which does not release the drug immediately after administration.

One example of delayed release formulation is the enteric coated formulations. Another subgroup of MR formulations is the Extended Release (ER) dosage forms, which are the focus of the present work. According to a definition from the U.S. Pharmacopeia (USP), ER formulations can be referred to as dosage forms that allow at least a twofold reduction in the dosing frequency compared to conventional dosage forms.7, 8 The interest in oral ER formulations has dramatically increased in recent years. In 1959 Robinson and Suedres made a formulation of sulfa methyl thiadiazole together with
hydrogenated castor oil, which was suspended in an aqueous vehicle, creating a formulation with extended drug release.\textsuperscript{9} Later, in the late 1950s and early 1960s Sjögren \textit{et al.} compressed active substances (e.g. pentobarbitone sodium and theophylline) together with polyvinyl chloride (PVC) and obtained extended drug release from these insoluble matrix tablets.\textsuperscript{10}

\subsection*{1.1 Biopharmaceutical Aspects on Oral ER Formulations}

The clinical effect of low molecular weight substance is often related to the concentration of the drug in the blood plasma. Classical blood plasma profiles for both immediate-release (IR) and ER formulations are shown in figure 1.1. It is well known that a drug only has a clinical effect when the concentration in the blood plasma is above the minimum effective concentration (MEC). If the concentration of the active substance is above the maximum safe concentration (MSC), the side effects will be unacceptable. The interval between the MEC and MSC is called the therapeutic window or therapeutic range and the time when the concentration is above the MEC is called the “duration” of the drug. The aim of ER formulations is to increase the time the substance is above its MEC by continuous release of the drug from the formulation. Under optimal conditions the rate limiting step in the drug absorption process of an ER formulation is its release rate, which then can be directly related to the concentration of the drug in the blood plasma. When the drug release rate from an ER formulation is constant, the blood plasma concentration will be constant under ideal conditions, whereas ER formulations with time dependent drug release rate may give rise to time variations in the concentration of the drug in the blood plasma (figure 1.1).
Figure 1.1: (a) Schematic picture of blood plasma concentration profile after administration of a drug to an individual, including the MSC, MEC, therapeutic range, and duration. (b) Repeated administration of IR formulation (four times daily) of a drug with short pharmacokinetic half-time and administration once daily of an ideal ER formulation with constant drug release (broken line) or ER formulation with non-constant drug release rate (dotted line). (Adopt from pharmaceutical manufacturing handbook)

The ER concept might offer several advantages, such as reduction in frequency of administration, reduction in side effects, less irritation in the gastrointestinal tract and improved patient compliance. Speers and Bonnano have also mentioned some economic aspects of ER formulations, such as the possibility to patent line extensions and to reduce manufacturing costs since fewer units are required to obtain the same effect. On the other hand, ER formulations may have several drawbacks, for example, large variations in effect between patients due to varying physiological factors within the patient group, limited transit time for the ER formulation, drug stability problems during the gastrointestinal passage and more severe complications such as dose dumping. The ER formulations can be a single unit, monolithic system or multiple-unit system containing many individual units with extended release. Multiple-unit system consists of many small pellets and are normally produced by extrusion and spheronization or coating on inert spheres. The composition and ER mechanism can vary for multiple-unit systems and some examples are membrane coated reservoir systems and polymer or lipid based matrix systems, where the matrices can be made of both soluble and insoluble carriers. From
a biopharmaceutical point of view, the multiple unit system has many advantages, such as more consistent gastrointestinal transit compared to larger monolithic systems. The gastrointestinal transit times for monolithic and multiple unit systems were compared in a study by Abrahamsson et al.\textsuperscript{19} It was found that the gastric emptying time for the small multiple units was considerably shorter than that of larger monolithic systems (on average 3.6 and 9.6 hrs. respectively). The transit times through the small intestine were approximately equal, whereas the transit time in the colon for the multiple units was longer compared to the monolithic system, which was explained by different influence of the motility on the different systems. Another advantage with multiple-unit compared to monolithic system is that the effects of dose dumping become less severe.\textsuperscript{20} A breakage and instant drug release from one pellet will have considerably lower effect than breakage of one monolithic system.

**1.2 Oral Controlled Release Systems\textsuperscript{21-25}**

There are more specialized groups of oral dosage form commonly referred as sustained release, extended release, long acting, gradual release, slow release dosage form. The scientific frame work required for successful development of oral drug delivery system consists of the basic understanding of following aspects.

- Physiochemical, pharmacokinetics and pharmacodynamic characteristics of a drug.
- Anatomical and physicomechanical characteristics of gastrointestinal track.
- Physicomechanical characteristics of drug delivery mode of the dosage form to be designed.

Oral controlled drug delivery is a system that provides continuous delivery of drug at a predetermined period throughout the course of GI transits.

Controlled drug release can be achieved by following classes of controlled drug delivery system.

1) Diffusion controlled system.
   A) Reservoir type
   B) Matrix type

2) Dissolution controlled system.
   A) Reservoir type
B) Matrix type

3) Diffusion and dissolution controlled release system

4) Methods using ion-exchange

5) Methods using osmotic pressure

6) pH independent formulations

7) Altered density formulations

1.2.1 Diffusion Controlled System

Basically diffusion process shows the movement of drug molecules from a region of higher concentration to one of lower concentration. The flux of the drug $J$ (in amount / area-time), across a membrane in the direction of decreasing concentration is given by Fick’s law.

$$J = -D \frac{dc}{dx}$$

$D$ = Diffusion coefficient in area / time

$dc/dx$ = Change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses core of a drug, it must diffuse through the membrane; the drug release rate $dm/dt$ is given by,

$$\frac{dm}{dt} = ADK C/L$$

Where: $A$ = Area

$K$ = Partition coefficient of drug between the membrane and drug core.

$L$ = Diffusion path length [i.e. thickness of coat].

$C$ = Concentration difference across the membrane.

This system is of two types which are discussed below.

A) Reservoir type

In this system, a water insoluble polymeric material encases core of a drug. The drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.
CHAPTER 1

INTRODUCTION

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Page 6

Figure 1.2: Schematic representation of diffusion controlled drug release: reservoir system.

**Description:** Drug core surrounded by polymer membrane that controls release rate.

**Advantages:** Zero order delivery is possible, release rates vary with polymer type.

**Disadvantages:** System must be physically removed from implant site, difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.

B) Matrix type

A solid drug is dispersed in an insoluble matrix and the rate of drug release is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

Figure 1.3: Schematic representation of diffusion controlled drug release: matrix system.
Higuchi has derived the appropriate equation for drug release from this system,
\[ Q = \frac{D}{T} \left[ 2A - Cs \right] Cst^{\frac{1}{2}} \]

Where:  
- \( Q \) = Weight in gm of drug released per unit area of surface at time \( t \)  
- \( D \) = Diffusion coefficient of drug in the release medium  
- \( Cs \) = Solubility of drug in release medium  
- \( T \) = Tortuosity of the matrix  
- \( A \) = Concentration of drug in the tablet, as gm/ml

**Description:** Homogenous dispersion of solid drug in a polymer mixture.  
**Advantages:** Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.  
**Disadvantages:** Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

A third possible diffusion mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat. The release rate can be given by the following equation.

\[ \text{Release rate} = \frac{AD}{L} = \left[ C_1 - C_2 \right] \]

Where:
- \( A \) = Area 
- \( D \) = Diffusion coefficient 
- \( C_1 \) = Drug concentration in the core 
- \( C_2 \) = Drug concentration in the surrounding medium 
- \( L \) = Diffusion path length

Thus, diffusion controlled products are based on two approaches, the *first approach* entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The *second approach* involves enclosing the drug particle with a polymer coat. In this case, the portion of the drug, which has dissolved in the polymer coat, diffuses through an unstirred film of liquid into the surrounding fluid.
1.2.2 Dissolution Controlled Systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as aspirin, a coating that dissolves in neutral or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve a useful function of directing drug release to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

A) Reservoir type

Drug is coated with a given thickness of coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true controlled release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thicknesses. Since the beads have different coating thicknesses, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at later times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate is synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

B) Matrix type

This is the more common type of dissolution controlled dosage form. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Two types of dissolution-controlled pulsed delivery systems are:
I) Single bead-type device with alternating drug and rate-controlling layer.

II) Beads containing drug with differing thicknesses of dissolving coats.

### 1.2.3 Diffusion and Dissolution Controlled Release System

In this system, drug core is enclosed in partially soluble membrane. The drug is released through the pores which are created in polymeric membrane due to dissolution of part of membrane. The amount of soluble polymer in coat will be the dominant rate controlling factor. An example of this type of system is polymer coating made up of ethyl cellulose and methylcellulose. The later dissolves and creates pores in the insoluble ethyl cellulose membrane, which allows the entry of aqueous media into the core and the dissolution of drug.

### 1.2.4 Methods Using Ion Exchange Resins

It is based on the formation of drug resin complex formed when an ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and is released with excess of $\text{Na}^+$ and $\text{Cl}^-$ present in gastrointestinal tract.

\[
\text{Resin}^+ - \text{Drug}^- + x^- \quad \rightarrow \quad \text{Resin}^+ - x^- + \text{Drug}^-
\]

Where $x^-$ is $\text{Cl}^-$, conversely,

\[
\text{Resin}^- - \text{drug}^+ + Y^+ \quad \rightarrow \quad \text{Resin}^- - Y^+ + \text{Drug}^+
\]

Where $Y^+$ is $\text{Na}^+$

These systems generally utilize resin compounds of water insoluble cross-linked polymers. They contain salt forming functional groups in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is controlled by the area of diffusion, diffusional path length and rigidity of the resin which is function of the amount of cross linking agent used to prepare resins. The release rate can be further controlled by coating the drug resin complex by microencapsulation process. The resins used include amberlite, indion, polysterol and others.
### 1.2.5 Methods Using Osmotic Pressure

A semi permeable membrane is placed around a tablet that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

**Description:** Drug is surrounded by semi permeable membrane and release is governed by osmotic pressure.

**Advantages:** Zero order release rates are obtainable. Reformulation is not required for different drugs. Release of drug is independent of the environment in which the system is placed.

**Disadvantages:** System can be much more expensive than conventional counterparts. Quality control is more extensive than most conventional tablets.

Two types of osmotically controlled systems are:

1. Type A contains an osmotic core with drug.
2. Type B contains the drug in flexible bag with osmotic core surrounding it.

### 1.2.6 pH - Independent Formulations

The gastrointestinal tract presents some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which is a constraint on the length of prolongation of drug release. Further the chemical environment throughout the length of gastrointestinal tract is a constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid, phosphoric acid or tartaric acid can be added to the formulation, to maintain a constant pH thereby rendering pH independent drug release. A buffered controlled release formulation is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to a suitable constant pH thereby rendering a constant rate of drug release.
e.g., propoxyphene in a buffered controlled release formulation, significantly increases reproducibility.

1.2.7 Altered Density Formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all, of its drug content is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

**High density approach**

In this approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1.4 gm/cm$^3$.

**Low density approach**

Globular shells, which have an apparent density, lower than that of gastric fluid.

1.3 Matrix Tablet

One of the least complicated approaches to the manufacturing of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown in table 1.1, which includes both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Hydroxy ethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly-ethylene oxide and cross-linked homopolymers and copolymers of acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.

There are three types of matrix tablets i.e.,

1. Hydrophilic matrices
2. Fat-wax matrices
3. Plastic matrices
Table 1.1 Examples of Different Types of Matrices

<table>
<thead>
<tr>
<th>Types of Matrices</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic matrices</td>
<td>Methylcellulose, Hydroxyethylcellulose, Hydroxypropyl- methylcellulose, Sodium carboxymethylcellulose, Carboxypolymethylene..</td>
</tr>
<tr>
<td>Fat-wax matrices</td>
<td>Carnauba wax, Stearyl alcohol, Stearic acid, cetyl alcohol, Triglycerides.</td>
</tr>
<tr>
<td>Plastic matrices</td>
<td>Polyethylene, Polyvinyl chloride, Ethylcellulose, Methylacrylate copolymer.</td>
</tr>
</tbody>
</table>

1.3.1 Hydrophilic Matrix Tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacturing and excellent uniformity of matrix tablets. Upon immersion, drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behaviour from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follows.

Cellulose derivatives: Hydroxy ethyl cellulose, Hydroxypropyl methylcellulose, Sodium carboxy methylcellulose.

Non-cellulose natural or semisynthetic polymers: Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of mannose and Galactose, Chitosan and Modified starches.

Polymer of acrylic acid: Polymer which is used in acrylic acid category is Carbopol.
1.3.1.1 Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is the most widely used release rate controlling polymer in hydrophilic matrices for extended release (ER) oral delivery systems. It provides robust versatile formulations and the possibility of simplified production. Different versions of commercially available HPMC is official in USP, IP and are available from various manufacturers. They are mostly distinguished by relative proportions of the hydroxy propoxyl and methoxyl substitutions. Increasing the proportion of hydrophilic hydroxy propyl group’s results in immediate hydration with a ranking order of Methocel®K > Methocel®E > Methocel®F. Generally, a rapid hydrating grade Methocel®K gets preference, particularly in case of water soluble drugs, where a rapid rate of hydration is essential to avoid burst release. Most often, a delayed or inadequate hydration of polymer leads to burst release and dose dumping (Dow pharmaceutical excipient, 1998).

For a fixed polymer level, viscosity of the selected grade of HPMC greatly influences the mechanical and diffusional properties of the matrix. Md. Mofizur Rahman et al., (2011) describe effect of various grades of hydroxypropyl methylcellulose matrix systems as oral sustained release drug delivery systems for ranolazine like E50, K100LV, Methocel K4M, K15M.42

Sumon R., et al., (2011) formulated matrix systems for oral sustained release drug delivery systems using different grades of hydroxypropyl methylcellulose (Methocel K4M, K15M, K100M and K100LV), in order to investigate the effect of diverse grades of these polymers on release mechanism from matrix tablets. Diclofenac sodium was used as a model drug to evaluate its release characteristics from different matrices.43

1.3.2 Fat-wax Matrix Tablet

The drug can be incorporated into fat wax granulations by spray congealing in an air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as
fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders.

The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

1.3.3 Plastic Matrix Tablet (hydrophobic matrices) 44,45

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials; provided the plastic material can be comminuted or granulated to the desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished as follows.

a. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.

b. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.

c. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses. For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene (Gothi et al., 2010).
1.4 Quality by Design (QbD)

Pharmaceutical is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. In order to do this, the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can be adapted to produce a consistent product over a period of time. Quality by design is an essential part of the modern approach to pharmaceutical quality. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. Implementation of QbD will enable transformation of the chemistry manufacturing and controls (CMC) review of abbreviated new drug applications (ANDAs) into a science-based pharmaceutical quality assessment.

1.4.1 Quality Risk Management (QRM)

Quality risk management is a key enabler for the development and application of QbD. During development, it enables resources to be focused on the perceived critical areas that affect product and process. It is one of the tools that provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It also facilitates continual improvement in the product and process performance throughout the product life cycle. Quality risk assessment in combination with the prior scientific and engineering knowledge helps in identifying material attributes and process parameters that can have a potential effect on the product critical quality attributes (CQAs). The tools used in risk assessment can help to identify and rank or prioritize parameters/attributes
that have a potential impact on the product CQAs. As one advances through the various phases of development and gains process/product knowledge, risk assessment enables the differentiation of true versus perceived risks. This in turn enables the efforts to be focused on the high-risk areas and develop strategies to mitigate them. 49

1.4.2 Quality Target Product Profile (QTPP)

The quality target product profile (QTPP) as defined in ICH Q8 (R1) is a summary of the quality characteristics or attributes of a drug product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product. 50, 51 For CR formulations, there may be more than one method to formulate the product to meet the same QTPP. Thus, between brand and generic, the formulation design may be different but the QTPP could be similar. A typical QTPP includes quantitative targets for attributes such as dissolution, potency, impurities, stability, release and other product-specific requirements. Depending on the type of controlled release, certain functionality related test(s) could be incorporated if they are important, for example, polymer viscosity, tortuosity, glass transition of composite and so on. For a generic CR product, bioequivalence is a quality attribute that is of extra significance.

The QTPP should typically include the following:

- Type of CR dosage form and route of administration, dosage form strength(s).
- Appearance, identity, size, ease of administration, patient population.
- Container closure.
- Therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed.
- Drug product quality criteria (e.g., sterility, purity) appropriate for the intended marketed product i.e. manufacturing considerations.

The target product quality profile (TPQP) is a quantitative surrogate for aspects of clinical safety and efficacy that has to be used to design and optimize a formulation and manufacturing process. International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI) calls this the Pharmaceutical Target Product Profile. Product specific examples include resuspendability for an oral
suspension, adhesion for a transdermal system and viscosity for a topical cream. Generic products include bioequivalence to the RLD as part of the TPQP. The TPQP is not a specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. The TPQP should include patient relevant product performance. For example, if particle size is critical to the dissolution of a solid oral product, then the TPQP should include dissolution but not particle size. Particle size would be a critical material attribute and thus included in the process description and control strategy. The TPQP should be performance based and not mechanism based.\textsuperscript{46,49}

1.4.3 Critical Quality Attributes (CQA)

A critical quality attribute is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit or distribution to ensure the desired product quality. CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in-process materials) and drug product. Drug product CQAs derived from the QTPP are used to guide the product and process development. Drug product CQAs are the properties that are important for product performance, i.e. the desired quality, safety and efficacy. Depending on the CR dosage form, these may include the aspects affecting the purity, potency, stability, drug release, microbiological quality and so on. CQAs can also include those properties of a raw material that may affect drug product performance or manufacturability. An example of this would be drug substance particle size distribution (PSD) or bulk density that may influence the flow of a granulation and therefore the manufacturability of the drug product. Similarly, the dissolution from a controlled release dosage form is dependent on the particle size of the polymer and the hardness of tablet. In this example, PSD and hardness can be designated as CQA’s.\textsuperscript{49,52,53}

1.4.4 Critical Process Parameter (CPP)

A parameter is a measurable or quantifiable characteristic of a system or process, while a process parameter is an attribute of the manufacturing system. Parameters are usually thought of as characteristics of equipment, processes or manufacturing systems (e.g., temperature, mixing speed, airflow), whereas attributes can be considered as
characteristics or properties of materials (e.g., melting point, viscosity and sterility). CPP is a process parameter whose variability has an impact on the critical quality attribute and therefore should be monitored or controlled to ensure that the process produces material of the desired quality. CPPs may change during the product life cycle as new knowledge is gained. For example, new CPPs may be identified in a unit operation in the manufacturing process of the drug substance or drug product or the acceptable range of values of a CPP may change based on the improved product and process knowledge. These changes may impact the registered manufacturing process or design space. It may be worth noting that for the same process you may have different set of CPPs. This is dependent on the type of product, the properties of the materials in the product and the desired characteristics of the product.

1.4.5 Design Space

The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes can be described in the design space. Selection of variables is done by the risk assessment and process development experiments can lead to an understanding of the linkage and effect of process parameters and material attributes on product CQAs and also help to identify the variables and their ranges within which consistent quality can be achieved. These process parameters and material attributes can thus be selected for inclusion in the design space. A description should be provided in the application of the process parameters and material attributes considered for the design space, those that were included and their effect on product quality.

The rationale for inclusion in the design space should be helpful to understand why some parameters were excluded. Knowledge gained from studies should be described in the regulatory submission. Process parameters and material attributes that were not varied through development should be highlighted.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subjected to regulatory assessment and approval. Because design space is potentially scale and equipment dependent, the design space determined at the laboratory scale may not be relevant to the process at the commercial scale. Therefore, design space
verification at the commercial scale becomes essential unless it is demonstrated that the design space is scale-independent. Currently, generic drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales. Sponsors may occasionally conduct these studies with appropriate design of experiments including multivariate interactions, which will create a design space at the laboratory or pilot scale. Such a design space, however, will have limited regulatory flexibility because the regulatory scientists will be unable to determine whether the design space is still valid at the commercial scale unless sponsors can provide additional information that shows the design space is scale-independent or actual verification data at the commercial scale. There is confusion among industry and regulatory scientists about the connection between design space and QbD. Many believe that, design space and QbD are interchangeable terms. This is incorrect. For generic drug applications, design space is optional. QbD can be implemented without a design space because product and process understanding can be established without a formal design space. It should be pointed out that implementation of QbD is strongly encouraged by FDA. For some complex drug substances or drug products, implementation of QbD is considered a required component of the application.

The development and refinement of the design space begins at product conceptualization and continues to evolve throughout the lifecycle of the product. At the time of filing a submission, the design space can be considered to be a snap shot in time representative of the current process knowledge. It continues to evolve as additional knowledge and information is generated during the commercialization of the product, which may lead to post-approval changes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. As such, the design space will require management under a company’s pharmaceutical quality system.

The creation of a design space begins with the definition of the Pharmaceutical Target Product Profile (PTPP), which identifies the desired performance characteristics of the product. Prior knowledge and a preliminary risk assessment can be used to identify experiments to be performed for the initial investigation into the importance of quality attributes and process parameters. The quality of raw materials (including API, solvents, starting materials, excipients and packaging components) should be assessed and any
critical quality attributes identified. As development continues, additional risk assessments can occur that define subsequent experiments that lead to an understanding of the interactions between different attributes and process parameters. In addition, multivariate models based on chemistry, biotechnology or engineering fundamentals can be used to build the design space.

1.4.6 Control Strategy
ICH Q10 defines control strategy as a planned set of controls derived from current product and process understanding that assure process performance and product quality. The controls can include the following.

- Parameters and attributes related to drug substance and drug product materials and components.
- Facility and equipment operating conditions.
- In-process controls.
- Finished product specifications.
- The associated methods and the frequency of monitoring and control.

The implementation of a control strategy inherently addresses the implementation of the design space. The control strategy for a product should be holistic and developed based on the impact of the changing characteristics of the product (e.g., powder blend to granulation to tablet) across the entire manufacturing process. The development of a robust control strategy facilitates greater process robustness and leads to lower variability in the process and the product. This in turn provides greater assurance of product quality and facilitates opportunities for real-time release of the product. It is important to understand that regulatory flexibility is the outcome of the enhanced process understanding and is not the goal of QbD. Controls are developed on the basis of the process understanding.
1.4.7 Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessment begins with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable.

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions and the concerns of stakeholders.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. Risk evaluation compares the identified and analyzed risk against given risk criteria. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help to identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability) and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium” or “low” which should be defined in as much details as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessment, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.
Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs

Risk assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.

Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality based on prior knowledge and initial experimental data. The initial list of potential parameters can be quite extensive, but can be modified and prioritized by further studies (e.g., through a combination of design of experiments, mechanistic models). The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to
accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process. The output/result of the quality risk management process should be appropriately communicated and documented. Communication might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidance.

1.4.8 Risk Management Methodology

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk. Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on; e.g., compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources. Additionally, the pharmaceutical industry and regulators can access and manage risk using recognized risk management tools and/or internal procedures. Below is a non-exhaustive list of some of these tools.
✓ Basic risk management facilitation methods (flowcharts, check sheets etc.)
✓ Failure Mode Effects Analysis (FMEA)
✓ Failure Mode, Effects and Criticality Analysis (FMECA)
✓ Fault Tree Analysis (FTA)
✓ Hazard Analysis and Critical Control Points (HACCP)
✓ Hazard Operability Analysis (HAZOP)
✓ Preliminary Hazard Analysis (PHA)
✓ Risk ranking and filtering
✓ Supporting statistical tools

It is appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., probabilistic risk assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.