Introduction

Oral administration has been the most versatile, convenient and commonly employed route of drug delivery. It is the most desirable and preformed method of administering therapeutic agents for systemic effect.

1.1. Oral controlled release dosage forms: An overview

An ideal dosage regimen in drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at a particular frequency. The frequency of administration or the dosing interval depends upon its half-life or mean residence time and its therapeutic index. In most cases, the dosing interval is much shorter than the half-life of the drug resulting in number of limitations associated with such a conventional dosage form. These limitations can be overcome by controlled release dosage forms.

1.1.1. Oral CRDDS: Introduction and development strategies

The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relied on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties. The basic goal of drug therapy is to achieve a steady-state blood concentration level within the therapeutic effective and non-toxic range for an extended period of time. The market for oral controlled drug delivery alone is expected to grow at 90% or more every year through 2007 [1].
Oral route was the most convenient route for the drug delivery. It received more attention in the pharmaceutical field because of more flexibility in designing of dosage form than the drug delivery design for other routes. The design for oral route depends up on various factors such as type of delivery system, the disease being targeted, the patient, the length of therapy and the properties of drug.

Most of the oral controlled drug delivery systems release the drug by diffusion, dissolution or combination of both mechanisms to release the drug in a controlled manner to the gastrointestinal tract. The physicochemical properties and biological properties of drugs the drug profile must be determined for the desired release rate of the drug from controlled release dosage form. Novel oral drug delivery systems are broadly classified into two categories such as controlled release dosage forms as well as targeting dosage forms. General controlled drug delivery preparations release the drug in a controlled manner in the GIT for systemic uptake and on particular area of GIT specified. In contrast, targeted preparations are releasing the drug in a specified area or tissue of the GIT (e.g. colon specific drug delivery systems).

1.1.2. Oral Controlled Release dosage forms vs. conventional systems

Over the years there has been an enormous amount of work put into designing of the drug delivery systems that can eliminate or reduce the clinical plasma concentrations which can be seen after the administration of conventional drug delivery systems to the patient according to specified dosage regimen. One of the first commercially available products to provide controlled release of a drug was dexedrine spansules, made by Smith
Kline and French in 1952. The Fig.1.1.2. indicates the comparison between the plasma drug concentration Vs time profile of immediate release and controlled release dosage forms.

![Graph showing plasma drug concentration over time for immediate release and controlled release dosage forms.](image)

**Fig. 1.1.2. Comparison between Plasma drug concentration – time profile of immediate release and controlled release dosage forms**

After this many more controlled release systems came into the market, some successful, others potentially lethal. A variety of terms was used to describe these systems:

*Delayed release* indicates that the drug is not being released immediately following administration but at a later time, enteric coated tablets, pulsatile-release capsules.

*Repeat action* indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.
**Prolonged release** indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

**Sustained release** (SR) indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.

**Extended release** (ER) dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 24 hours).

**Controlled release** (CR) dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.

**Modified release** (MR) dosage forms are defined by USP as those drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional forms, whereas an extended release (ER) dosage form allows a twofold reduction in dosing frequency or increase in patient compliance or therapeutic performance. It is interesting to note that the USP considers the terms controlled release, prolonged release and sustained are interchangeable with extended release [2].
1.1.3. Reasons for oral CRDDS

There is a clinical need to develop CR formulations to improve the drug therapy over conventional counterparts, especially in the following cases:

I. Short elimination half-life \( (t_{1/2}) \) and minimum effective concentration \( (MEC) \) required for the therapy.

   Shorter the half-life of a drug, larger will be the fluctuations between the maximum safety concentration \( (C_{ss \, max}) \) and minimum effective concentration \( (C_{ss \, min}) \) upon multiple dosing. If the MEC is therapeutically required, either frequent dosing of a conventional drug product or development of a CR product is necessary.

II. Relatively long elimination half-life \( (t_{1/2}) \), and either wide or narrow therapeutic range or small fluctuation desired at steady state.

   The drugs having reasonably long elimination half-life may also need to be formulated as CR products mainly for:

   - Two or three day extension and
   - To minimize the fluctuations between \( C_{ss \, max} \) and \( C_{ss \, min} \) with narrow therapeutic range drugs.

1.1.4 Advantages of oral CRDDS

   Oral delivery is the most preferred method for the introduction of therapeutic agents. Patients are usually accustomed to orally delivered drugs and find the method
non-invasive. Unfortunately, this drug delivery route is not always compatible with therapeutic compounds because the drug must enter the gastrointestinal tract.

Many drugs have been formulated or reformulated to overcome this limitation. Oral controlled-release (OCR) formulations have many advantages over conventional products.

*Improved therapeutic efficacy* – Reduction in drug plasma level fluctuations; maintenance of steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

*Reduced side effects* – Drug plasma levels are maintained and improve the tolerability within a narrow range without any fluctuations. This greatly reduces the possibility of side effects.

*Patient compliance* – Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

*Reduced health care cost* – The total cost of therapy of the controlled release product could be comparable or lower than the immediate-release product. With reduction in side effects, the overall expense in disease management also would be reduced.

1.1.5 Limitations of Oral CRDDS

- On the other hand oral CRDDS suffer from a number of potential disadvantages:
  
  - Relatively poor *in vitro-in vivo* correlation
- Possible dose dumping

- Reduced potential for dose change or withdrawal in the event of toxicity

- Loss of effect in conditions like diarrhoea (too fast transit time)

- Poor CR formulation with the drugs having:
  - Extensive first pass metabolism (except prodrugs)
  - Extremely short elimination half-life (low therapeutic index)
  - Extremely long elimination half-life (narrow therapeutic index)
  - Bioavailability problems
  - Instability in GI environment

1.1.6 An ideal candidate for CRDDS

The desired biopharmaceutical characteristics of drugs to be used in the development of oral CR dosage forms are:

**Biopharmaceutical parameters:**

- Molecular weight : <1000mg

- Solubility : > 0-1 mcg/ml at pH 1 to 7.8

- pKa : non-ionized moiety>0.1% to 1% at pH 1 to 7.8

- Apparent partition coefficient : 0.5 to 2.0
• General absorbability: from all GI segments

• Release: should not be influenced by pH and enzymes

• Stability: stable in GI environment

• Protein binding: less

To evaluate whether the drug is a suitable candidate or not for the design of *per* oral CR formulations, one must consider the following pharmacokinetic parameters of the drug.

*Pharmacokinetic parameters*

• Elimination half-life, \( t_{1/2} \): preferably between 0.5 and 8 hours.

• Total clearance, \( Cl \): Should not be dose dependant

• Elimination rate constant, \( K_{el} \): required for the design

• Apparent volume of distribution, \( V_d \): the larger the \( V_d \) and MEC, the larger will be the required dose size. The maximum dose that is to be incorporated into oral CR formulations is about 500mg. the smaller the \( V_d \), the easier is the incorporation of drug into dosage form.

• Absolute bioavailability, \( F \): should be 75% or more

• Absorption rate, \( k_a \): must be much greater than the release rate
• Therapeutic concentration, $C_{av}^{ss}$: the lower the $C_{av}^{ss}$ and the smaller the $V_d$, the lesser is the amount of drug required.

1.1.7 Technologies for the development of CRDDS

A number of technologies were developed for the formulation of CRDDS. Various designs and their probable release mechanisms were listed in table 1.1.

Table 1.1 Various designs and their probable release mechanisms for CR Formulations

<table>
<thead>
<tr>
<th>S.No.</th>
<th>DESIGN OR TYPE OF THE SYSTEM</th>
<th>RELEASE MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dissolution controlled CR systems</td>
<td>The dissolution of drug from system</td>
</tr>
<tr>
<td></td>
<td>• Encapsulation (including microencapsulation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Barrier coating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Embeded into a matrix of fatty material</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Repeat action coating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Coated plastic materials or hydrophilic materials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Matrix dissolution control</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Diffusion controlled CR systems</td>
<td>The diffusion of the drug solution through a water-insoluble, permeable polymeric film</td>
</tr>
<tr>
<td></td>
<td>• Reservoir devices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Matrix devices</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Dissolution and diffusion controlled CR systems</td>
<td>Diffusion of a drug solution through a porous matrix</td>
</tr>
<tr>
<td></td>
<td>• Non disintegrating polymeric matrix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hydrophilic matrices</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ion-exchange resin CR systems</td>
<td>Ion-exchange between the resin-drug complex and ions in the GI tract</td>
</tr>
<tr>
<td>5</td>
<td>pH-independent formulations</td>
<td>Influenced by change in pH and ionic permeability of the membrane coating</td>
</tr>
</tbody>
</table>
Osmotically controlled CR systems

They contain the buffering agents in a system which maintains constant pH throughout the GIT, so that the drug release from the device is not affected by variable pH of the GIT. Water entering by osmosis dissolves the drug, and the drug solution is forced out through a laser drilled orifice.

Altered-density systems

Diffusion through high-density systems or from floating devices.

1.2 Biopharmaceutical classification system

The biopharmaceutical classification system (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is proven to be a valuable tool for the regulation of changes in oral drug products during scale-up and after product approval. When combined with the dissolution of the drug product, the BCS takes three major factors into account that govern the rate and extent of drug absorption from IR solid oral dosage forms. They are dissolution, solubility, and intestinal permeability \(^3\). According to the BCS, drug substances are classified as follows:

- **Class 1**: High Solubility – High Permeability
- **Class 2**: Low Solubility – High Permeability
- **Class 3**: High Solubility – Low Permeability
- **Class 4**: Low Solubility – Low Permeability
Class Boundaries

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a bio waiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

C. Dissolution

In this guidance, an IR drug product is considered *rapidly dissolving* when not less than 85% of the labeled amount of the drug substance dissolves within 30 minutes,
using *U.S. Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or simulated gastric fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or simulated intestinal fluid USP without enzymes.

**Solubility determination**

- pH solubility profile of test drug in aqueous media with a pH range of 1 to 7.5
- Shake flask or titration method
- Analysis by a validated stability-indicating assay.

**Permeability determination:**

Extent of absorption in humans:

- Mass-balance pharmacokinetic studies
- Absolute bioavailability studies

Intestinal permeability methods:

- *In vivo* intestinal perfusion studies in humans
- *In vivo* or in situ intestinal perfusion studies in animals
- *In vitro* permeation experiments across epithelial cell mono layers
Dissolution determination

- USP apparatus I (basket) at 100 rpm or USP apparatus II (paddle) at 50 rpm.

- Dissolution medium (900 ml) of 0.1 N HCl or simulated gastric fluid, pH 4.5 buffer, and pH 6.8 buffer or simulated gastric fluid.

- Compare dissolution profiles of test and reference products using a similarity factor (f<sub>2</sub>).

Table 1.2 Examples of orally administered drugs<sup>[4]</sup>

<table>
<thead>
<tr>
<th>CLASS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Paracetamol, Metoprolol, Pseudoephedrine, Theophylline</td>
</tr>
<tr>
<td>Class II</td>
<td>Carbamazepine, Glibenclamide, Ketoconazole, Griseofulvin</td>
</tr>
<tr>
<td>Class III</td>
<td>Acyclovir, Atenolol, Cimetidine, Ranitidine</td>
</tr>
<tr>
<td>Class IV</td>
<td>Chlorothiazide, Furosemide</td>
</tr>
</tbody>
</table>

1.3 Dissolution modeling as applicable to controlled release products

1.3.1 Modeling and comparison of dissolution profiles

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of time, t or Q=f(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson-Crowell, Weibull, Higuchi, Banker-Lonsdale, Korsmeyer-Peppas and Hopfenberg models. Other release parameters, such as dissolution time (t<sub>x%</sub>), assay time (t<sub>x min</sub>), dissolution efficacy (ED), difference
factor \((f_1)\) and Rescigno index \((\xi_1 \text{ and } \xi_2)\) can be used to characterize drug dissolution / release profiles.

A water soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water-soluble drug the self-erosion of the matrix will be the principle release mechanism. To accomplish these studies, the cumulative profiles of the dissolved drug are more commonly used in opposition to their differential profiles. To compare dissolution profiles between two drug products, model dependant (curve fitting), statistical analysis and model independent methods can be used.

**Mathematical models (curve fitting)**

1. **Zero order kinetics**

\[
Q_1 = Q_0 + k_0 t
\]

Where \(Q_1\) is the amount of drug dissolved in time \(t\), \(Q_0\) is the initial amount of drug in the solution (most times, \(Q_0 = 0\)) and \(K_0\) is the zero order release constant.

\[
f_t = K_0 t
\]

Where \(f_t = 1 - (W_t/W_0)\) and \(f_t\) represents the fraction of drug dissolved in time \(t\) and \(k_0\) the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

**Use:** This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms and osmotic systems\(^5\) etc. The pharmaceutical dosage forms following this profile release the same
amount of drug by unit of time. It is the ideal method of drug release in order to achieve prolonged pharmacological action.

2. First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969).

\[ \log Q_t = \log Q_0 + K_1 \frac{t}{2.303} \]

Where \( Q_t \) is the amount of drug released in time \( t \), \( Q_0 \) is the initial amount of drug in the solution and \( K_1 \) is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior \(^6\), in such a way, that the amount of drug released by unit of time diminishes.

3. Higuchi model

\[ F_i = K_H \sqrt{t} \]

Where \( K_H \) is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based on the Fick’s law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical
dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs \[7,8\].

4. Hixson-Crowell model

Hixson and Crowell (1931) recognized that the particle regular area is proportional to the cubic root of its volume, derived an equation that can be described in the following manner:

\[ M_0^{1/3} - M_t^{1/3} = K_s t \]

Where \( M_0 \) is the initial amount of drug in the pharmaceutical dosage form, \( M_t \) is the remaining amount of drug in the pharmaceutical dosage form at time \( t \) and \( K_s \) is a constant incorporating the surface-volume relation. This expression applies to the pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. When this model is used, it is assumed that the release rate is limited by the drug particle’s dissolution rate and not by the diffusion that might occur through the polymeric matrix. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution \[9\].
5. Korsmeyer-Peppas model

Korsmeyer et al. (1983) developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time (t):

$$F_t = at^n$$

Where $a$ is a constant incorporating structural and geometric characteristics of the drug dosage form, $n$ is the release exponent, indicative of the drug release mechanism, and the function of $t$ is $M_t/M_\infty$ (fractional release of drug).

If the diffusion is the main drug release mechanism, a graphic representing the drug amount released, in the referred conditions, versus the square root of time should originate a straight line. Under some experimental situations, the release mechanism deviates from the Fick’s equation, following an anomalous behaviour (non-Fickian). In these cases a more generic equation can be used:

$$M_t/M_\infty = at^n$$

This model is generally used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

### Table 1.3 Interpretation of diffusion release mechanisms from polymeric films.

<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Drug transport mechanism</th>
<th>Rate as a function of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>$t^{-0.5}$</td>
</tr>
</tbody>
</table>
0.5 < n < 1 | Anomalous transport | \( t^{n-1} \)
--- | --- | ---
1.0 | Case II transport | Zero order release
> 1 | Super case II transport | \( t^{n-1} \)

When there is the possibility of a burst effect, b, this equation becomes (Kim and Fassihi, 1997) \(^{10}\): \( M_t/M_\infty = a t^n + b \)

In the absence of lag time or burst effect, l and b values would be zero and only \( a t^n \) is used. This mathematical model, also known as the Power law, has been used, very frequently, to describe the drug release from several different pharmaceutical modified release dosage forms \(^{10,11,12}\).

1.4 Multiparticulate systems as oral controlled release drug delivery systems

Multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to obtain different release patterns as well as reproducible and short gastric residence time. Multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations.

Types of Multiparticulates

- Pellets
- Granules
- Mini tablets
- Micro particles (Micro sphères or Microcapsules)
- Nanoparticles

**Advantages of multiparticulates**

- Multiparticulates can be divided into desired doses without formulation and process changes
- They can be blended to deliver simultaneously incompatible bioactive agents or particles with different release profiles at the same sites within the gastrointestinal tract.
- When taken orally, multiparticulates generally disperse freely in the gastrointestinal tract
- Multiparticulates have maximum absorption and minimized side effects
- They reduce inter and intra patient variability

Pelletization is one of the most widely used techniques for the development of CRDDS.

### 1.4.1 Pellets

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended orally for oral administration. Pellets can be prepared by many methods. Among all, the compaction and drug layering techniques being the most widely used today.
Regardless of which manufacturing process is used, pellets have to meet the following requirements \[^{13}\]:

- They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
- The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 µm.
- The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within the limits.

**Pellets have their position for many reasons:**

Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a surface area-to-volume ratio. Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form \[^{14}\].

The pelletized product can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage
system. The pelletized product can freely disperse in G.I tract\textsuperscript{[15, 16, 17]} as a subunit, thus maximizing drug absorption and reducing peak plasma fluctuation. Consequently, potential side effects can be minimized without impairing drug bioavailability. Local irritation derived from high local concentrations of a drug from a single-unit dose, can be avoided.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for the delivery of drug at a specific site within the gastrointestinal tract or to sustain the action of drug over an extended period of time. With pellets, the above mentioned goals can be obtained by the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect\textsuperscript{[18, 19, 20, 21]}. The advantage of multi-unit products as a controlled-release dosage form is believed to be their behavior in \textit{in vivo} because of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics. The transit time of a gastrointestinal drug delivery system along the gastrointestinal tract is the most limiting physiological factor in the development of a controlled-release gastrointestinal drug delivery system targeted to once-a-day medication\textsuperscript{[22]}. Gastro-intestinal transit time, greatly affects the bioavailability of a drug from an orally administered controlled release preparation\textsuperscript{[23]}. Gastric transit of both single and multiple-unit solid dosage forms is prolonged in a fed stomach compared to a fasting one. Plastic spheres of 7mm remained
in the food-filled stomach even as food itself expelled steadily \cite{7, 24}. Once the stomach had emptied, the spheres began to transit in clusters \cite{25}.

It has been reported that pellets smaller than about 2.4 mm in diameter, are free from the digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach. A maximum pellet diameter of 1.5mm has been recommended for an optimal multiple-unit formulation \cite{7, 26}. Devereux 1987 clearly showed that the threshold size must be below 1mm. According to Khosla et al., \cite{15, 16, 27} there is no actual cut-off size for gastric emptying, but as the size of the pellets increase, predictable emptying from the fed stomach becomes uncertain and highly variable. However, it has been demonstrated that gastric emptying is not only dependent on the size but also on some other important factors, such as density of pellets \cite{22}, nature of food \cite{26} and inter-subject variation \cite{7}. Clarke et al., 1993 \cite{28} and Tuleu et al., 1999 \cite{29} showed that both density and size of the pellets affect gastrointestinal transit time. The higher density of the pellets prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time. Controversial results have also been reported to the effect of pellets densities on the transit times through the gastrointestinal tract.

### 1.4.2 Theory of pellet formation and growth

In order to judiciously select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth.
Different theories have been postulated which are related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are confined to visual observations \[^{30}\]. Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing \[^{31}\]. As the conventional granulation, the most thoroughly studied, most classified pelletisation process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions such as nucleation, coalescence, layering and abrasion transfer \[^{31}\].

Nucleation is a common stage in all pelletisation/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form a three phase i.e., air-water-liquid nuclei and are attached by liquid bridges which are pendular in nature \[^{32}\]. The bonding strength is improved by reduction of particle size. The sizes of the primary particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates, influenced the size, rate and extent of nuclear formation \[^{32}\]. Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation \[^{31}\].

Nucleation is followed by a transition phase, and growth mechanisms affect the transition region during coalescence and layering \[^{33}\]. Coalescence is defined as the formation of large sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess of moisture on the nuclear surface \[^{33}\]. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering is a slow growth mechanism and involves the
successive addition of fragments and fines on an already formed nucleus \(^{[32]}\). In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction that occurs due to attrition, breakage and shatter \(^{[32]}\). The fines and the fragments that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favorable collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached \(^{[32]}\).

In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of materials from one granule to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particle. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist \(^{[32]}\).

**1.4.3 Methods of preparing pellets**

The most commonly used pelletization techniques are:

- Solution layering
- Suspension layering
- Powder layering and
- Extrusion-spheronization
Other techniques that are used occasionally are

- Balling
- Spray congealing and drying
- Cryopelletization and
- Melt Spheronization

Compaction and drug layering are the most widely used pelletization techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Fig 1.4 indicates the process of pelletization by extrusion-spheronization. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer\textsuperscript{[34]}. Of the drug layering techniques, solution layering, suspension layering and powder layering are widely used. Other pelletization methods, such as globulation, balling, cryopelletization and compression are also used in the development of pharmaceutical pellets although in a limited scale\textsuperscript{[32]}.

1.4.3.1 Extrusion-Spheronization

Extrusion-Spheronization is a multiple-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheronizer to produce a spherical shape, drying the wet pellets in a dryer and finally, screening to achieve the required size distribution\textsuperscript{[35, 103]}. The granulation step can be performed both in batch-type processors,
including a conventional high-shear and sigma-blade mixers, and in continuous mixers, such as Nica M6 instant, and high-shear twin-screw mixer-extruders.

Extruders for the extrusion process have been classified generally as screw, sieve and basket, roll and ram extruders. Based on the type of feed mechanism used to transport the mass towards the die, they have been broadly classified as screw, gravity or piston type extruders. Most spheronizers have been designed based on a revolving grooved plate driven by a variable speed drive unit at the base of a smooth-walled drum. The drum capacity, plate diameter and plate design may vary. In order to increase the capacity of the spheronization stage, a continuously working spheronizer has been introduced. The process produces products ranging from barely-shaped, irregular particles like the conventional granulation, to very spherical particles with drastically different properties [24].

Tableting characteristics can be altered by modifying the composition, the granulating fluid or the process conditions [36]. The main advantage over other methods of producing drug-loaded spheres or pellets is the capacity to produce spherical pellets of uniform size and high drug content up to 90% [36].

Recently, different types of fluidized bed rotary processors have been developed more successfully for preparing compaction-type pellets such as the extrusion-spheronization process in a one-step process. This technique has solved many problems related to the multi-step extrusion and spheronization process. They are consuming less time, requiring lower labor costs and less space [60].
Fig. 1.2. Process of pelletization by solution or suspension layering

Fig. 1.3. Process of pelletization by powder layering
1.4.3.2 Drug layering

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powders on nuclei which may be crystals or granules of the same material or insert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. Fig 1.2 indicates the process of pelletization by solution/ suspension layering. In powder layering, complete dissolution does not occur, due to low liquid saturation, irrespective of the solubility of the active agent in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared insert seeds, followed by the addition of powder. Fig 1.3 indicates the process of pelletization by powder layering.
Conventional pan coaters have been used from the very beginning of the history of drug layering pelletization. From the economic point of view, however, use of conventional pan coaters is not very reasonable due to the higher labor costs and time consumption, and lower yield. An important disadvantage of pan coaters is the shortage of process control \cite{32, 39}. More recently modified forms of pan coaters have been developed, which resolves many of the drawbacks related to the old system \cite{38}.

The problems of drug layering pelletization by conventional pan coaters had led to the development of two types of rotary granulators (fluidized-bed and centrifugal granulators), respectively. These devices offer many advantages including lower manufacturing costs, flexibility of operation and ease of automation \cite{32}. Centrifugal granulators can be used for manufacturing multiple-unit, immediate or controlled – release drug products for oral use \cite{14, 39}.

Through the use of these systems, initial beads can be prepared and subsequently drug-layered and coated in the same equipment, resulting in highly spherical multi-layered and coated in the same equipment, resulting in highly spherical multi-layered granules with adequate controlled-release characteristics.

### 1.4.3.3 Other pelletization methods

Other pelletization methods such as globulation, agitation and compaction are used, although in limited scale, in the preparation of pharmaceutical pellets \cite{32}.
**Globulation, or droplet information**, consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or solution without excipient are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs[^32].

**Spray congealing** is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets[^32]. Both immediate- and controlled-release pellets can be prepared in this process depending on the physicochemical properties of the ingredients and other formulation variables[^106].

**Compression** is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing[^40].

Balling is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid[^32].

[^32]: References for specific processes and techniques.
[^106]: Further reading for formulation variables impacting the quality of pellets.
1.4.4 An overview of fluid bed coating process

Batch-type fluid bed processes for pharmaceutical manufacturing have been in use for more than 40 years. Originating in Europe, this technology gradually found its way into U.S. manufacturing facilities, beginning with the use of fluid bed dryers. The first dryer showed immediate superiority over conventional tray drying ovens and soon attracted considerable interest from manufacturing personnel. The introduction of an expansion space between the product container and the filter chamber, and the inclusion of a liquid-spray nozzle in that space, gave rise to fluid bed agglomeration (more commonly referred to as fluid bed granulation) – an effective alternative to conventional low shear mixing and tray drying [41]. The fluid bed coaters are mainly classified into three categories. They are:

1.4.4.1 Top spray coating

This process is used for general coatings right up to enteric coating. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which are introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (counter current) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform.

Coating in the continuous fluid bed is particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve
bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones. Coated and dried particles are continuously extracted (Glatt-technology, fluid bed coating)\[^{42}\].

This type of coating is widely used for the granulation process for the manufacture of tablets. The principle involved in the granulation process is as follows. During fluid bed granulation, the granules are usually not formed by the binder itself, as often anticipated, but by the spray liquid, whereas the binder consolidates the originally formed agglomeration. Granulate growth is controlled by moisture control of the product bed when a certain quantity of liquid has been sprayed onto the substrate, a first agglomeration can be observed.

### 1.4.4.2 Bottom spray coating (Wurster coating)

This process is particularly suitable for a controlled release of active ingredients. In the wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a wurster cylinder and a base plate with different perforation, the particle to be coated are accelerated inside the wurster tube and fed through the spray cone concurrently. As the particles continue travelling upwards, they dry and fall outside the wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated.
Bottom spray coating (continuous fluid bed)

Particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones whereby spraying can take place from below in the form of a bottom spray. Coated and dried particles are continuously extracted.

1.4.4.3 Tangential spray coating (Rotor pellet coating)

This process is ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of rotor method.

When an organic system is used, the success of the process will depend on the selection of the appropriate fluid-bed dryer. The bottom-spray and tangential spray fluid-bed coaters appear to perform satisfactorily. However, the top-spray fluid bed coater does not appear to be the optimal choice because of the distance and direction the coating solution must travel before coming in contact with the substrate and because the heat of vaporization tends to be lower for an organic solvent than for water [18].
1.4.5 Characterization of pellets

Pellets with rapid drug release are seldom delivered (supplied) as a finished product without using an extra coating. The pellets are mainly coated for aesthetic, taste masking, stability, and enteric-release or controlled-release purposes. The coating thickness of pellets must be uniform in order to achieve any of these end product performances. For uniform coating thickness, the formulation, equipment and process variables are usually selected based on the reproducibility of morphologic properties of the pellets.[43]

1.4.5.1 Size distribution

The size distribution of pellets should be as narrow as possible due to the following reasons:

- For acceptable film coating, a narrow size distribution of pellets is a prerequisite (in addition to spherical shape and smooth surface). The size distribution affects both the performance of the coating and the release rate of the drug.[21] A narrow size distribution will ensure minimum variation in coating thickness throughout the batch of pellets and therefore result in a uniform performance of pellets within the batch.[43].

- Segregation is a common occurrence in capsule-filling and tablet compression due to the wide size distribution of pellets and thus results in variations in content uniformity and/or dosage form performance.
• A narrow particle size distribution improves (facilitates) the blending process in blending different types of pellets or different batches of pellets \(^{[43]}\).

The size distribution of pellets is determined by different methods. The most common and widely used method is sieve analysis \(^{[37]}\). The reasons for its extensive use are simplicity, lower costs, low time consumption and low turnover of operators. Sieve loading, type of motion (vibratory tap), intensity and duration of intensity are recognized critical variables. In spite of the simple and easy technique, sieving has some disadvantages such as screen skewing particle size data to the inability of the sieve to detect variation in the shapes of particles.

Another widely used method of measuring the size distribution of pellets is microscopy. The main advantage of this method over most other methods of sieve analysis is the particle profile itself is measured rather than some property which is dependent on the particle size. Optical microscopy has been developed for particle size analysis from simple eyepiece graticules to fast device projectors and comparators, and the latest popular computerized method of image analysis \(^{[40]}\). Scanning electron microscopy can also be used for measuring the size of the pellets. Both types of microscopic techniques are tedious and time consuming, since a large number of particles need to be measured individually to make a size-frequency distribution plot. In addition, variation in the generated data is possible among operators. Another method developed for the measurement of pellet size distribution is laser diffraction. This method is most suitable for spherical particles \(^{[39, 44]}\).
1.4.5.2 Shape and surface roughness

One of the important objectives of pellet preparation (pelletization) is to produce spherical and smooth particles, suitable for subsequent successful coating, i.e., optimal for controlled-release products. Moreover, spherical particles help the transfer of materials due to their good flow characteristics. Good spherical properties are useful in processes that require an exact metering of granules such as capsule filling \[^{45}\]. Different methods have been proposed for measuring the shape and surface roughness of the pellets. The commonly used method is the analysis of microscopic or non-microscopic pictures of object of interest. However, the most widely accepted advanced technique is optical microscopy with image analysis. The direct measurement of surface roughness/smoothness by the image analysis \[^{46}\] method is not sensitive enough. Instead, fractal geometry of particle obtained by microscopy with image analysis is used for the measurement of surface smoothness of pellets \[^{45}\]. In pharmaceutical field, fractal geometry has mainly been used in the study of surface roughness of powders, either excipient or drugs. Since it has been revealed that powder or granule characteristics like flow and packing properties, are also related to the smoothness of the particle surface, knowledge about the smoothness of pellet surface is important. Electron microscopy (SEM) is the technique of choice for measuring the shape and surface smoothness of the pellets to support visually the other qualitative and quantitative results \[^{13,44}\].

1.4.5.3 Surface area

The characteristics of pellets, those controlling the surface area, are mainly size, shape, porosity and surface roughness. Knowledge of the surface area of pellets is
desirable especially if film coating is considered. Because the thickness of the film applied to pellets in a sustained-release-type dosage form dictates the rate at which drug is released, knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area available \[45\].

There are three methods of measuring the surface area of pellets. It can be calculated from the particle-size distribution by measuring/using the mean diameter. However, this calculation does not account for the contributions of the surface area arising from other morphologic characteristics, such as porosity, surface roughness and shape of pellets. Therefore, two techniques, i.e. gas adsorption and air permeability permit direct calculation of surface area.

Quick and simple, air permeability methods are widely used pharmaceutically for specific surface measurement, especially to control batch to batch variations. The principle resistance to the flow of a fluid – such as air – through a plug of compacted material is the surface area of the material. The applicability of air permeability methods for pellets is not highly acceptable since the flow rate through the plug or bed is also affected by the degree of compression of the material. The gas adsorption method (commonly known as the BET method) was developed by Brunauer, Emmett and Teller. In this method the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is measured at different pressures, and the results are plotted as \(P/V\) (\(p_0-p\) versus \(p/p_0\) to generate a linear plot where \(V\) is the volume of gas in \(cm^3\) adsorbed per gram of substrate at pressure \(p\) and \(p_0\) is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield
the values $b$ and $V_m$. The specific surface ($s_w$) of the pellets is then obtained by using the following equation.

$$S_w = 4.35^*V_m$$

**1.4.5.4 Porosity**

The porosity of pellets influences the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. It also affects film deposition and formation during coating. The porosity of the pellets can be measured qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry \[13, 34, 45\]. The porosity of pellets can be determined quantitatively also by optical microscopy and scanning electron microscopy together with image analysis.

**1.4.5.5 Density**

The density of pellets can be affected by changes in the formulation and/or process, which may affect other process or factors, such as capsule filling, coating, and mixing. Variation of density from batch to batch affects the potency of the finished capsule, causes problem in batch size determination during coating and produces segregation during mixing.

The bulk density of the pellets can be measured by an automatic tapper. It is an indicative of the packing properties of particles and, therefore, is greatly influenced by the diameter and the size distribution of the pellets. True density indicates the extent of densification or compactness of substances. The true density of pellets can be determined
by an air-comparison pycnometer, a helium pycnometer or by the solvent displacement method [47].

1.4.5.6 Friability

The essential requirement of pellets is to have an acceptable friability to withstand further processing, especially the subsequent coating. A high amount of attrition during the coating procedure could modify the release behavior due to the incorporation of small particles in the film [32]. A friability of less than 0.08% is generally accepted for tablets, but for pellets this value could be higher due to the higher surface area/unit and subsequent involvement of frictional force [14].

1.5 INTRODUCTION TO NON STEROIDAL ANTI INFLAMMATORY DRUGS (NSAID’s)

All drugs grouped in this class have analgesic, antipyretic and anti-inflammatory actions in different measures. In contrast to morphine they do not depress central nervous system (CNS), do not produce physical dependence, have no abuse liability and are weak analgesics (except for inflammatory pain). They are non-narcotic, non-opioid or aspirin-like analgesics. They act primarily on peripheral pain mechanisms, an also in the CNS to raise pain threshold. They are more commonly employed and many are over-the-counter drugs.

Classification of NSAIDs

- Non-selective COX inhibitors (traditional NSAIDs)
  - Salicylates: Aspirin
• **Propionic acid derivatives:** Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen

• **Anthranilic acid derivatives:** mephenamic acid

• **Aryl-acetic acid derivatives:** Diclofenac, Aceclofenac

• **Oxicam derivatives:** Piroxicam, Tenoxicam

• **Pyrrole-pyrrole derivatives:** Ketorolac

• **Indole derivative:** Indomethacin

• **Pyrazolone derivatives:** Phenyl butazole, Oxyphenbutazone

• **Preferential COX-2 inhibitors**
  
  Nimesulide, Meloxicam, Nabumetone

• **Selective COX-2 inhibitors**
  
  Celecoxib, Etoricoxib, Parecoxib

• **Analgesic-antipyretics with poor anti-inflammatory action**

  • **Para amino phenol derivative:** Paracetamol (Acetaminophen)

  • **Pyrazolone derivatives:** Metamizol (Dipyrone), propiphenazone

  • **Benzoxazocine derivative:** Nefopam

**NSAIDs and prostaglandin (PG) synthesis inhibition**

The major mechanism of action of NSAIDs is PG inhibition. Prostaglandins, prostacyclin (PG I₂) and thromboxane A₂ (TXA₂) are produced from arachidonic acid by
the enzyme cyclooxygenase which exists in a constitutive (COX-1) and an inducible (COX-2) isoforms; the former serves physiological ‘housekeeping’ functions while the latter, normally present in minute quantities, is induced by cytokines and other signal molecules at the site of inflammation. Generation of PGs locally mediate many of the inflammatory changes. However, COX-2 is consecutively present at some sites in the brain ans in juxtaglomerular cells and may serve physiological role at these sites. Most NSAIDs inhibit COX-1 and COX-2 non-selectively, but now some selective COX-2 inhibitors have been produced. Fig 1.5 shows the mechanism of action of Non-steroidal anti-inflammatory drugs.

**Fig. 1.5 Mechanism of action of NSAIDs**