Chapter 1.

Introduction
1 Introduction

There is now a growing realisation that innovative delivery of drugs would not only increase safety and efficacy levels but also improve the overall performance of the drug. While drug delivery plays an important role in enriching drug performance, researchers are concentrating on using delivery as a means to reduce dosage frequency, preferably through non-invasive methods. The oral route is the most dominant route for drug delivery. Amongst the various formulations for controlled drug delivery used orally, the multiple-unit systems are gaining popularity and their market presence has increased several folds in the last several years.

1.1. Multiple-Unit Systems

Multiparticulates are discrete particles that are combined into one dosage unit to form a multiple-unit system. The are also defined as pharmaceutical-containing particles having a diameter ranging from about 0.3 to 1.5 mm. They may exist as pellets, granules, sugar seeds (nonpareils), minitablets, ion-exchange resin particles, powders and crystals with drugs being entrapped in or layered around cores. Multiparticulates are commonly filled into capsule shells and less commonly compressed into tablets.

1.1.1. Advantages of Multiple-Unit Systems

Multiple-unit systems have several advantages over single-unit systems such as non-disintegrating tablets or capsules —
1. **Greater flexibility of dosage form design and development:** Coated drug pellets can be presented in the form of suspension, filled into capsules or compressed into tablets.¹

2. **Ease of coating:** Drug pellets, because of their spherical shape, have lowest surface-to-volume ratio and therefore in comparison to granules, they provide an ideal shape for the application of film-coating.⁵

3. **Ease of capsule filling:** Spherical shape of pellets enable them to flow freely and pack uniformly thereby alleviating handling and packaging problems⁶ and allow reproducible fill weights and uniformly in drug content in capsules.²

4. **Improved elegance, product identification and patient compliance:** Drug pellets can be given an outer coating of different colours that distinguish one drug from the other and these can then be blended and filled into transparent hard gelatin capsules. This improves elegance and facilitates better acceptability and compliance of the product by the patient. Moreover, the differently coloured/coated drug pellets can be blended with a suitable direct compression vehicle and compressed into tablets without destroying the integrity of barrier coating.

5. **Controlled delivery of drugs for oral use:** Pellets can be designed as:
   a) **Continuous Release Systems:** Capsules containing a large number of pellets having release because of the composition or amount of coating applied, provide sustained effect over a period of time. Such systems show better therapeutic performance than single unit controlled-release formulations like tablets.⁵
   b) **Delayed Transit and Continuous Release Systems:** The residence time of drug in the stomach and/or intestine can be prolonged by altering the density of drug particles. This is possible through the use
of drug pellets having density greater than 1.6 g/cc (by incorporation of heavy inert materials like barium sulphate, titanium dioxide, iron oxide, etc.) or having density less than that of gastrointestinal fluids (hydrodynamically balanced, low density pellets).\textsuperscript{7,9}

c) **Delayed Release Systems:** Pellets can be specifically coated to control the site of drug dissolution in the gastrointestinal tract.\textsuperscript{10} Enteric-coated pellets of diameter less than 1.0 to 1.5 mm pass the pyloric sphincter even when it is closed thereby showing rapid drug absorption in comparison to enteric-coated tablets\textsuperscript{11}. Pellets coated with pH-sensitive polymers that release the medicament only at the alkaline pH of colon can be used to target drugs such as mesalamine to colon or effect systemic absorption of protein and peptide drugs like insulin and vasopressin from colon.

6. **Ease of design of controlled-release formulations containing more than one drug:** If more than one drug are used in the formulation, pellets of different drugs with a suitable barrier coating to obtain the desired release profile can be prepared separately and then combined together into the same dosage form.

7. **Ease of drug dissolution and analysis:** By loading each drug onto the pellets separately, the dissolution and assay for each can be carried out separately without interference from other drug(s). Moreover, if any batch of drug is found to be deficient with respect to its dissolution profile or assay, it can be adjusted or discarded without the loss of other drug in the formulation.

8. **Greater stability of chemically incompatible drugs:** Non-compatible drugs can be pelletized separately, blended and formulated in a single dosage form or formulated into the same pellet by situating the active
substances in different layers and/or by separating the layers from others by coatings.\textsuperscript{10}

9. **Ease of dose divisibility:** Preparations containing controlled-release pellets may also be subdivided without accelerating drug release thereby facilitating adjustment of individual doses without formulation and process changes.\textsuperscript{12}

10. **Greater safety and efficacy of drugs:** Small size of pellets enables them to disperse freely in the gastrointestinal tract and high local concentrations of inherently irritating or anesthetic agents can be avoided. Moreover, their exposure to large surface area promotes complete and uniform absorption, minimize peak plasma fluctuations and thus reduce the potential for systemic side-effects.\textsuperscript{2}

11. **Lowered tendency for dose dumping:** By subdividing the multiple-dose onto many pellets, the possibility of barrier failure and subsequent release of the entire drug at the same time is significantly reduced in comparison to controlled-release tablets.\textsuperscript{13}

12. **Reproducibility of plasma profile and therapeutic effect:** Pellets reduce variations in gastric emptying rates and transit times thus minimizing intra- and inter-subject variability in plasma profiles, which are common with single-unit regimens. Moreover, controlled-release drug pellets are less susceptible to dose dumping in comparison to single-unit controlled-release formulations such as tablets and enable the therapeutic effect to be reached in a predictable and reproducible fashion with a lower risk of side effects.\textsuperscript{2}

13. **Marketing edge:** Controlled-release pellet products help the pharmaceutical companies in creating line extension of their product
range, extend patent protection, globalize product and overcome competition.\textsuperscript{14}

Some examples of multiple-unit systems are described in figure 1.1.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{multiple_unit_systems.png}
\caption{Examples of different multiple-unit systems}
\end{figure}
1.2. Objectives for Coating of Multiparticulates

Multiparticulates may be coated for following reasons—

1. To design controlled-release drug delivery system.\textsuperscript{1,18}
2. To prepare delayed- or enteric-release dosage form.\textsuperscript{18}
3. To reduce the incidence and severity of dose-related systemic and local adverse-effects.\textsuperscript{1,15}
4. To improve patient compliance through reduction of dosing frequency and incidence of side-effects and better control of disease condition.\textsuperscript{18}
5. To enhance oral bioavailability of poorly aqueous soluble drugs.\textsuperscript{15}
6. To enhance the physical characteristics of multiparticulates by enhancing flow and reducing friability.\textsuperscript{15}
7. To mask unpleasant colour, taste or odour and prevent leaching of core materials from the multiparticulates thereby improving patient acceptance of the product.\textsuperscript{4,15,16}
8. To enhance the stability of acid-labile, photo-labile, oxidation-labile, moisture-sensitive or hydrolysis-labile drugs – coats may serve as barriers that protect incompatible or unstable core materials from one another and from environmental elements such as light, oxygen, water and carbon dioxide.\textsuperscript{15,16}
9. To enhance the aesthetics of the dosage form.\textsuperscript{18}
10. To facilitate the identification of product and different dosage strengths of same product.\textsuperscript{18}
11. To extend patent protection, overcome competition and create brand loyalty.
1.3. Controlled-Release Coated Multiparticulates

Coating of multiparticulates with a rate-controlling film is one method of obtaining controlled-release (CR) dosage form. CR dosage forms are normally designed to have composite effects of both an immediate-release dose and an extended-release dose which together allow drugs to be delivered at a predetermined rate over a fixed time period.\(^1\) This permits improved treatment of many diseases by preventing systems breakthrough (which occurs when plasma drug concentration falls below the minimum effective concentration), reducing dosage frequency and improving patient compliance.

An appropriately designed controlled-release drug-delivery system (CRDDS) can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required (see figure 1.2).

Size, shape and coating thickness of CR coated multiparticulates are variable. Sizes of multiparticulates usually range from 0.3 to 2 mm,\(^3\) with functional coats having a thickness of 5 - 50 μm.\(^\text{17}\)
Figure 1.2. A hypothetical plasma concentration-time profile from conventional multiple dosing and an ideal controlled drug delivery formulation.

The most common shape of individual cores for the development of CR multiparticulate systems is a sphere since –

1. A spherical shape has minimum surface-to-volume ratio thereby requiring minimum coating on weight percent basis for obtaining a desired drug release profile.

2. Spherical shape enables easy processing, especially coating of particles at a rapid rate with a more uniform deposition of applied coating.

3. Spherical shape offers a consistent and definite surface for uniform drug release.

Coats formed from various polymeric coating materials are broadly classified as –

1. Polymeric solutions
2. Aqueous polymer dispersions\textsuperscript{19} 
3. Molten polymers,\textsuperscript{20} and 
4. Dry powders.\textsuperscript{21-23}

Depending upon the type of coating material used, following functions are achieved—

1. Controlled-release 
2. Targeted-release 
3. Delayed-release (enteric-release) 
4. Pulsatile-release 
5. Taste/colour/odour masking 
6. Improved stability (to pH, oxidation, hydrolysis and/or light) 
7. Improved bioavailability.

1.4. Methods for Preparing Multiparticulate Cores

Pellets and granules are commonly used as cores for CR coating of multiparticulates. These days, micron-sized particles are also used.\textsuperscript{24-26}

1.4.1. Pelletization

Pellets or spherical granules may be produced by—

- Drug layering, or
- Extrusion/spheronization.
Drug layering onto nonpareil seeds can be carried out in one of the three ways (see figure 1.3.) –

1. Drug solution layering
2. Drug suspension layering, and
3. Drug powder layering.

In the former two processes, drug solution or suspension containing a suitable binder is sprayed onto nonpareil seeds in a fluidized-bed or coating pan. The solvent is evaporated by the hot fluidizing air leaving layers of non-volatile material on the surface. Alternatively, powder layering of drug can also be done onto the surface of nonpareil seeds in a coating pan or centrifugal granulator.

In extrusion/spheronization (see figure 1.4.), a wet mass of powder or molten drug and/or excipients is extruded through a perforated screen to form cylindrical extrudates which are spheronized on a friction plate into pellets and subsequently dried/congealed.
Figure 1.3. The three methods of drug layering on nonpareils seeds
(a) Three main types of extruders

(b) Spheronizer/marumerizer

(c) Steps involved in pelletization by extrusion/spheronization

*Figure 1.4. Preparation of drug pellets by extrusion/spheronization*
1.4.1.1. Properties of Ideal Pellets

Ideal drug pellets should possess following properties –

1. They should be near spherical in shape and have a smooth surface, both considered optimum characteristics for subsequent film-coating.

2. The particle size range should be as narrow as possible for following reasons –

   a. 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. 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.

   b. 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.

   c. A narrow particle size-distribution improves (facilitates) the blending process in mixing different types of pellets or different batches of pellets.

3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.
1.4.2. Granulation

Granules may be produced as extrudates of wet powder mass\textsuperscript{31} or by microagglomeration of powders using the fluid-bed granulator (see figure 1.5.a).\textsuperscript{32,33} In the latter, binder solution is sprayed onto a bed of powder suspended in fluidizing air, causing agglomeration.\textsuperscript{34} There are many other methods of granulation including high shear granulation (figure 1.5.b),\textsuperscript{33,35} steam granulation,\textsuperscript{36-37} roller compaction (figure 1.5.c),\textsuperscript{38-40} pressure swing granulation,\textsuperscript{41,42} hot melt granulation,\textsuperscript{43-45} tumbling melt granulation\textsuperscript{46} and fluidized-bed hot-melt granulation.\textsuperscript{47} The granulation conditions of each method and characteristics of the granules produced are different. Hence, the appropriate method is chosen to suit the materials to be granulated and to produce granules with the desired properties.

1.4.3. Spray Drying

The spray dryer and spray coater can produce micron-sized particles that are suitable as multiparticulate cores.\textsuperscript{46} In spray drying, a solution or suspension is sprayed via an atomizing air nozzle placed at the top of a hot chamber (see figure 1.6). The solvent within the droplets evaporates in the hot environment during the downward fall to leave dried particles which are collected at the bottom of the chamber.\textsuperscript{17,47,48}

1.4.4. Spray Congealing

In spray congealing, molten waxes, lipids or fats are sprayed via an atomizing nozzle placed at the top of a cold chamber (see figure 2.6). The spray may be co-current or counter-current to the cooling air stream. The sprayed droplets solidify during the downward fall to form particles which are collected at the bottom of the chamber.\textsuperscript{49-52}
a. Granulation method of pelletization

b. High shear mixer used in wet/melt granulation

c. Roll compaction used in dry granulation

*Figure 1.5.* Granulation method of pelletization
1.5. Methods for Preparing Coated-Multiparticulates

Various methods exist for the coating of multiparticulates –

1. Air-suspension coating\textsuperscript{24,53,54} which is the most common method
2. Compression coating\textsuperscript{55}
3. Microencapsulation techniques – the three most commonly employed microencapsulation methods are

   a. Solvent evaporation,\textsuperscript{56}
   b. Coacervation,\textsuperscript{57} and
   c. Interfacial condensation.\textsuperscript{58}

There is an increasing interest in the area of small particle coating, whereby methods such as spray drying\textsuperscript{59,60} and spray congealing\textsuperscript{52} are explored to produce micron-sized coated-particles.
1.5.1. **Air Suspension Coating**

Air suspension coating is also known as fluid-bed coating whereby liquid coating material is sprayed onto a bed of cores suspended in fluidizing-air (see figure 1.7). Hot fluidizing air dries the liquid coats while cold fluidizing air coagulates the molten coats to leave a thin film over the cores. Coating materials may be aqueous polymeric dispersions,\textsuperscript{24,53} polymer solutions\textsuperscript{64} or polymer melts\textsuperscript{62} each having a different mechanism of film formation. For aqueous polymer dispersions, discrete polymer particles in the liquid layer come into close contact as water evaporates. Capillary action leads to deformation and coalescence of polymer particles to form a continuous film.\textsuperscript{63} For polymeric solutions, the dissolved polymer increases in concentration as the solvent evaporates, polymer particles become immobile and leave a thin film around cores.\textsuperscript{64} For molten materials, finely atomized molten liquid is sprayed onto core particles which spread and congeal to form a continuous solidified film around cores.\textsuperscript{20}

1.5.2. **Powder Coating**

Powder coating is an alternative technique to the use of polymer solution or suspension for multiparticulate coating.\textsuperscript{21} Here, powder mixture (e.g. polymer and talc) and liquid composition (e.g. plasticizer and binder) are fed through separate inlets and sprayed onto a bed of fluidizing cores. The liquid composition enables the powder mixture to adhere to the cores. Powdered polymer particles are subsequently cured to enable complete coalescence of polymer particles for film formation.\textsuperscript{21,22} Powder coating is commonly done in tangential spray fluid-bed coating device or centrifugal granulator (see figure 1.8). Powder coating is faster than liquid-based coatings because small amounts of water are used with the plasticizer thus reducing the drying phase.\textsuperscript{21,22} However, the coats obtained in this method were found to be more permeable and had pores more than those obtained with conventional
organic polymer solutions or aqueous polymer dispersions. This results in the requirement of higher coating level to produce a similar rate of drug release.

1.5.3. Compression Coating

Compression coating is more suitable for larger multiparticulates such as minitablets. This method requires the use of tablet press whereby a core is placed on a powder bed of coating in a die, covered with a top layer of coating powder and the tablet is pressed by the punch to form a coated particle.\(^{55}\) This method is not commonly used for coating of multiparticulates because of complex mechanism used in the tablet press. There is also the possibility of incomplete or uneven coating when the core is not placed properly.\(^{3}\)

1.5.4. Microencapsulation

Solvent evaporation, coacervation and interfacial condensation are some microencapsulation methods used to coat multiparticulates. These methods are not popular because of their inefficiencies. Other microencapsulation methods include spray drying and spray congealing, whereby the coated microparticles are produced under appropriate conditions.

1.5.4.1. Solvent Evaporation

In solvent evaporation, the coating polymer is dissolved in a volatile organic solvent and the cores placed in the polymer solution. Constant stirring facilitates the evaporation of the solvent leaving a film-coat around the cores (see figure 1.9).\(^{56}\)
Figure 1.7. Air suspension coating process

Figure 1.8. Tangential spray fluid-bed/CF granulator for powder coating
Figure 1.9. Schematic overview of the four principal process steps in microsphere preparation by solvent extraction/evaporation

1.5.4.2. Coacervation

In coacervation, cores are placed in a polymer solution. Polymer particles are precipitated onto the cores by a change in temperature or by adding a precipitating agent. The coated particles are then separated and dried.57
1.5.4.3. **Interfacial Condensation/Complexation**

Interfacial complexation involves the interaction of components of the coating solution and core surfaces to form complexes leaving a polymeric coat on the surface of the cores.\(^9\)

1.5.4.4. **Spray Drying**

Spray drying can be used to produce either microcapsules or microspheres in which drugs are coated with polymer dissolved or dispersed in a polymer matrix, respectively (see figure 1.10.a). The type of microparticle obtained was found to be dependent upon the solubility of drug in the coating material. Microspheres are produced by spray drying the coating solutions in which the drug is soluble. If the drug is insoluble in the coating solution, microcapsules are produced.\(^9\)

1.5.4.5. **Spray Congealing**

Spray congealing is a solvent-free method that can be used to produce microcapsules (see figure 1.10.b). High encapsulation efficiency, spherical shaped particles with CR properties can be obtained by using the appropriate type and amount of melttable material. Spray congealing may not be suitable for hydrophilic drugs such as verapamil because of the poor encapsulation rate. This problem may be tackled by using a more hydrophilic wax such as stearyl alcohol and/or a surfactant such as soya lecithin.\(^32\)

1.6. **Mechanisms of Drug Release from CR Coated Multiparticulates**

Drug release\(^7\) from CR coated multiparticulates may occur by –

1. Diffusion
2. Osmosis, and
3. Polymer erosion (see figure 1.11).
A combination of these mechanisms usually occurs in every system, with each contributing to a different extent. From drug-release studies of coated planar matrices, drug loading, diffusivity ratio and coating thickness were found to be the most important factors controlling drug release. This showed that diffusion was the most dominating mechanism in those systems.

On contact with aqueous environment, water enters the core and dissolution of the drug within the core takes place. This allows the drug to diffuse through the core and coat into the dissolution medium. Diffusion may take place through the polymer phase, plasticizer channels and aqueous pores (figure 1.11.a).

With osmotic cores, drug release is driven by the osmotic pressure generated by the influx of water. The osmotic pressure may also cause the coat to expand and form pores, which allows the movement of drug out of the core (figure 1.11.b).

For erodible polymer coats, erosion of the coat starts to occur the moment the coated multiparticulates are exposed to an aqueous environment (figure 1.11.c). As the core drug concentration decreases during drug release, the thickness of the coat decreases simultaneously, maintaining the drug-release rate. This delicate balance can result in a constant rate of drug release.
a. Microencapsulation by spray drying

b. Microencapsulation by spray congealing

*Figure 1.10.* Spray drying/congealing methods of preparing microcapsules

a. Diffusion  

b. Osmosis  

c. Erosion

*Figure 1.11.* Principal mechanisms of drug release from coated multiparticulates
1.7. Factors Affecting the Preparation of CR Coated Multiparticulates and their Drug-Release Characteristics

1.7.1. Characterisation of Cores

1.7.1.1. Physical Properties

In general, thicker coats release drugs at slower rates than thinner coats.\textsuperscript{67,68} The surface area of a batch of multiparticulates determines the amount of coating material needed to produce coats with a particular thickness. Surface area is determined by size, shape and surface roughness of the cores.

Smaller cores have higher surface area-to-volume ratios and require more coating material to achieve a similar coat thickness as larger cores of an equivalent volume.\textsuperscript{67} In the Wurster process, this may be attributed to the different fluidizing patterns and velocities of differently sized cores. Smaller particles fluidize higher and suspend longer in the expansion zone, reducing the cycling rate. They are also accelerated faster in the Wurster column resulting in a shorter time spent in the spray zone.\textsuperscript{69} However, different air suspension coating equipment has produced conflicting results, whereby pellet size was found to have variable influence on the thickness of coats.\textsuperscript{70,71}

Spherical particles have the lowest surface area to volume ratios compared with other shapes. They do not have any protuberances that can affect flow and, hence, are equally exposed to the coating spray to enable the formation of a uniform coat. On the other hand, needle-like cores are less evenly coated as the surfaces are unequally exposed to the coating spray. They tend to be friable and produce fines that may be embedded in the film coat during film-formation. Embedded fines may leach out from the coat during dissolution, creating pores, which allow easy drug passage and faster
drug release. All these factors contribute to a slower drug-release rate from spherical cores than other shapes.\textsuperscript{72}

Cores with rougher surfaces tend to develop more uneven coats than equivalent sized smoother particles.\textsuperscript{73} Uneven, raised ridges receive thinner coats which have lower mechanical strength and a greater tendency to stretch or break from internal stress. This may lead to failure of the coat to achieve a sustained-release.

Porosity of cores can affect the film-formation process when aqueous polymeric dispersions are used. Pores may retain liquid by capillary forces and slow down the evaporation of solvent during film-formation. This hinders the coalescence of polymer particles resulting in a more porous coat with a faster drug-release profile.\textsuperscript{70}

1.7.1.2. Drug Properties
The concentration of drug within cores and coats may influence drug-release rates.\textsuperscript{74,75} When the drug concentration in the cores is high, increased drug dissolution and migration into the film occur during coating. Embedded drug particles can form pores within the coat, increasing the drug-release rates. High concentrations of drug on the surface of cores also increase interaction of drug with the polymer coat, resulting in poorer film adhesion.

Drug-release rates may be affected by the physical properties of drug particles. Drugs that are highly water-soluble and have small molecular sizes, increase drug-release rates by dissolving and diffusing quickly,\textsuperscript{76,77} whereas large insoluble complexes reduce drug-release rates by hindering drug movement across films.\textsuperscript{78}
Chemical reactivity of drugs can also affect the drug-release rates. Some drugs may react with coating preparation of certain pH and chemical composition. Some of these reactions include salt formation, complexation, ester hydrolysis, ring opening, or cyclization. The resultant drugs decrease drug-release rates especially if they are poorly soluble or large in size. 

1.7.1.3. Excipient Properties

Core excipients with high osmolarity build up osmotic pressure when liquid permeates into the cores. The osmotic pressure generated drives the movement of dissolved drug out through aqueous pores or laser orifices, contributing to drug release. However, if the osmotic pressure is too strong, CR coats may rupture leading to burst-release of core materials.

Excipients with high water solubility increase water content in the cores on contact with the dissolution media. This facilitates drug dissolution and hence increase the rate of drug-release from cores. Excipients with low water solubility may also increase the drug release rate. The low miscibility with water prevents proper film-formation during coating. The resultant coats have poor integrity and may release the drug faster. Poor film adhesion to the cores may hasten the disintegration of the CR coats resulting in burst release of core contents.

During spheroidization, different excipients may result in cores with different sphericity, hardness and density. Excipients with higher spheroidizing abilities produce spheroids with slowest drug-release rates. This was observed in ethylcellulose coated cores containing various fillers (microcrystalline cellulose, maize starch, calcium hydrogen phosphate, glucose and lactose). The coated-cores were found to have increasing drug-release rates according to the order listed. Microcrystalline cellulose had the
highest spheromizing ability and produced cores with slowest drug-release rates.\textsuperscript{80}

1.7.2. Characterisation of the CR Coat

1.7.2.1. Physical Properties of the Coat

The viscosity of the CR coating preparation is dependent on the solid content, type and molecular weight of polymers used. Viscous coating preparations have poorer flow properties and may increase the tendency for the nozzle(s) to clog and core particles to agglomerate during the coating process. They are also difficult to spread on cores, hindering coalescence of the coat resulting in poorly formed CR coats.\textsuperscript{81}

The thickness of the coat determines the path length for drug diffusion. Generally, thick coats lower drug release rates\textsuperscript{75,78,82} and increase lag times.\textsuperscript{83} However, thicker coats may have increased brittleness and can rupture if the internal stress is very high leading to potential dose-dumping problems.

1.7.2.2. Components of the Coat

1.7.2.2.i. Solvent

Volatile organic solvents have been widely used for coating purposes in the past. However, since the 1970s the use of organic solvents for coating formulations has gradually lost favour and been replaced by water. This was as a result of the toxicity concerns, danger of explosion, fear of environmental pollution, and occupational health hazards for workers with the use of organic solvents.\textsuperscript{3,15} The use of water as a solvent for coating applications has led to problems of its own. Water has a higher heat of vaporisation than volatile organic solvents and requires longer drying times at higher temperatures. This may be detrimental to heat and moisture-
sensitive drugs. Aqueous coating preparations were also found to require a higher amount of coating material than organic solvents to achieve the same drug-release profile. This was attributed to the higher tendency of the aqueous coating preparations to form porous coats.

1.7.2.2.ii. Polymer

There are many types of polymers that can confer coatings with CR properties. They may be classified according to their origin as being natural, semi-synthetic or synthetic. Natural polymers include zein, alginate, chitosan, pectin, shellac and rosin. Semi-synthetic polymer includes ethylcellulose, cellulose acetate and hypromellose (HPMC). Synthetic polymers include methacrylic acid copolymers.

Natural polymers and their derivatives are advantageous as coating materials because of their low toxicity. Synthetic polymers often contain residual monomers, plasticizers, softeners and fillers which need to be carefully evaluated for their potential toxicity. The most commonly used polymers for CR coatings of multiparticulates are ethylcellulose, methacrylic acid copolymers and cellulose acetate.

Different polymers may impart different drug release profiles. A blend of two or more polymers may be used to provide a larger spectrum of physicochemical properties by enhancing film flexibility and drug-release profiles.

Different grades of polymer used can also affect the drug-release rates. As the molecular weight of a polymer increases, the mechanical strength also increases until the critical molecular weight beyond which the mechanical properties do not improve further. This was observed in ethylcellulose-coated spherical granules where low molecular weight grades
formed films with cracks and flaws resulting in loss of CR properties and high molecular weight grades were able to slow the drug-release rates.\textsuperscript{101}

1.7.2.2.III. Plasticizers

Plasticizers increase film elongation, decrease elastic modulus and decrease tensile strength of the polymers by lowering glass transition temperatures. They can be added to polymers to form softer and more pliable polymer coats. The suitability of a plasticizer depends upon its ability to interact with the polymer chains.\textsuperscript{102}

Plasticizers enhance the incidence of flaws and cracks in CR coats especially for cores that swell on contact with water.\textsuperscript{53} Loss of plasticizers from the polymer coat through evaporation (permanence) and migration to the cores or migration into packaging materials may cause the coats to become brittle and form cracks, which allow a faster release of drugs from the cores. However, high plasticizer levels may result in increased agglomeration during coating because of the ease with which the coat deforms.\textsuperscript{103}

Plasticizers can be classified as polyols (e.g. glycerol, propylene glycol, polyethylene glycol (PEG)), organic esters, (e.g. phthalate esters, dibutyl sebacate, citrate esters, triacetin) or oils/glycerides (e.g. castor oil, acetylated monoglycerides, fractionated coconut oil). Recently, \(\alpha\)-alkanyl succinic anhydrides were found to be effective plasticizers for ethylcellulose coating preparations.\textsuperscript{104}

Drug release is affected by the type, amount, molecular weight and concentration of plasticizers used. Lipophilic plasticizers may reduce the drug-release rate from osmotic cores by delaying the swelling of polymer coats.\textsuperscript{83} Increased amounts of plasticizers may reduce permeability of the
coat to water and result in reduced drug-release rates. Plasticizers with high molecular weight may reduce drug-release rates by decreasing the moisture permeability of the coats. High concentrations of plasticizers may increase the mechanical strength of the films formed.

1.7.2.2.iv. Water-Soluble Additives
Water-soluble materials may be added to coating formulations to enhance the rate of drug-release. Water-soluble low molecular weight compounds include sucrose, lactose, sorbitol, sodium chloride and calcium phosphate, which dissolve in aqueous media and leach out from the coating membrane forming pores. Porosity modifiers with larger particle sizes, smaller specific surface areas, greater hygroscopicity coefficients or higher solubilities may form more aqueous channels, increasing drug-release through CR coats. While pores may cause an increase in drug-release rates, the effect may be short-lived as pores close over time, especially if drug release takes place above the minimum film-forming temperature.

Water-soluble high molecular weight compounds include PEG, PVP, HPMC and HPC, which may hydrate in aqueous media but not completely leach out from the coating. This forms channels, which increases the permeability of the coat. Increased permeability by water-soluble additives may also be a result of the swelling of the coats.

1.7.2.2.v. Colorants
Colorants may be water-soluble dyes or water-insoluble pigments. Pigments are considered to be superior to dyes because they are chemically more stable and have higher opacity, which enhances protection against light. Pigments may be added for their anti-tack properties or as indicators of coating uniformity.
At low pigment concentration, the permeability of the coat to water and air is not affected. Increasing the concentration of pigments beyond the critical pigment volume concentration may cause detrimental effects in mechanical properties, appearance and permeability of the coats.\textsuperscript{113}

Certain colorants may not be compatible with the type of coating preparation used. Aluminium lakes are not compatible with aqueous polymeric dispersions. On contact with ionic polymers of aqueous polymeric dispersion, aluminium lakes release electrolytes which cause aggregation of some polymer particles. On contact with non-ionic polymers of aqueous polymeric dispersions, the surface charges of aluminium lakes change, causing them to aggregate.\textsuperscript{114}

1.7.2.2.vi. **Anti-Tack Agents**

Anti-tack agents are materials capable of reducing agglomeration or sticking of particles during the coating process. Magnesium stearate, talc and kaolin are common anti-tack agents. Other anti-tack agents include soluble-salts, plasticizers and film formers. These components may also influence the drug-release rates from coated particles.

Talc may increase the lag time of drug release. It does so by increasing diffusional resistance hence reducing water permeability of the film-coating.\textsuperscript{83} Other anti-tack agents such as magnesium stearate, stearic acid and silicon dioxide increase drug release rates when their concentration exceed the critical pigment volume concentration. At those concentrations, there is insufficient polymer to bind the insoluble particles, resulting in the increased formation of pores.\textsuperscript{115}

Sodium chloride\textsuperscript{116} and sodium citrate\textsuperscript{117} are soluble-salts which display anti-tack properties. Both salts suppress agglomeration in pellets
coated with HPMC by reducing the viscosity of HPMC coating material. They do so by precipitating the HPMC polymers. However, in this process, the formation of pores is enhanced resulting in higher drug-release rates.

Plasticizers such as PEG, triacetin, triethyl citrate, and film formers such as vinylpyrrolidone/vinyl acetate co-polymers and PVP can be used as anti-tack agents.\textsuperscript{118} PEG can also be used as an overcoat to prevent agglomeration of multiparticulates and to enhance flow.\textsuperscript{119} Recently, PVP was found to be superior to PEG as an anti-tack agent under similar conditions because of its greater viscosity-lowering effect.\textsuperscript{120} When using these anti-tack agents, it must be noted that the drug-release profiles may be affected as a result of formation of plasticizer channels, which facilitate drug release.

1.8. Processing Equipment for Coating

Basic coating equipment consists of a coating chamber, nozzle(s), pump(s), exhaust filter(s) and retaining filter(s). Constant developments to improve the current coating equipments have led to a vast diversity of equipment setups. Each setup has different coating efficiencies and may be suitable for coating different types of cores.\textsuperscript{121,122}

1.8.1. Pan Coaters

The first coating chambers were spherical-shaped coating pans and tapered cylindrical pans, which have poor thermal contact with drying air that is blown onto the surface of the particle bed and does not reach the particles under the surface. Drying capacity was improved by installing better exhaust systems and using immersion swords. This led to the development of perforated pans and a suspension coating system which increased the efficiency of coating (see figure 1.12).
1.6.2. **Fluid-Bed Coaters**

An account of air-suspension coating or fluid-bed coating of multiparticulates is given by Jones and Percec. In the Wurster process, rotary-granulator and top-spray granulator, the coating materials are applied onto a fluidized substrate bed using nozzles located at the bottom, side or top of the coating chamber, respectively (see figure 1.13). Developments to the traditional Wurster process resulted in the Wurster HS and Precision Coater. The Wurster HS has a spray nozzle placed further from the substrate bed, reducing the attrition caused by the high atomizing air velocities from the nozzle. The Precision Coater has a proprietary swirl accelerator, which swirls and accelerates the air within the coating chamber, improving coating uniformity and drying of the coated particles during coating.

1.9. **Processing Variables for Coating**

1.9.1. **Coating Temperature**

Unsuitable bed temperatures contribute to the formation of poor-quality films. There is an optimal temperature whereby drug release from CR coated pellet is slowest. At this temperature, water evaporation takes place at a rate that is slow enough for adequate coalescence of polymer spheres but fast enough to minimize drug migration and dissolution in the liquid layer.

At low temperatures, longer time is required for drying and this allows soluble drug to migrate out from the cores into the liquid layer. The dissolved drug reduces the surface tension of the liquid layer, lowering the capillary forces required for deformation and coalescence of polymer particles. Drugs embedded in the film may dissolve on contact with dissolution media resulting in a porous and more permeable coat. If the temperature is lower than the minimum film-forming temperature (MFT), polymer particles may dry before coalescing forming discontinuous porous films.
Figure 1.12. Perforated pan coating device for coating of multiparticulates

a. Top-spray

b. Bottom-spray/Wurster

c. Tangential-spray

Figure 1.13. The three different multiparticulate coating fluid-bed devices
Higher temperatures favour coating as particles dry faster and have enhanced mobility. However, when the temperature is too high, evaporation of water may be so fast that it does not allow development of capillary pressure required for the coalescence of polymer particles. This results in formation of discontinuous porous films. High temperature may also increase the drying of atomized droplets before they reach the cores. This phenomenon is often referred to as spray-drying effect and results in less coating material being deposited on the particles, forming thinner coats. Spray-dried particles may also be embedded in the film coats, disrupting the film.\textsuperscript{126}

1.9.2. Fluidizing Air-Flow Rate

Fluidizing air-flow distributes cores within the coating chamber and exposes them to the spray material. It also serves to dry the liquid film-coat deposited on the cores during coating. Low air-flow rates may not provide enough drying capacity and result in high agglomeration rates. However, high air-flow rates may increase the erosion of friable cores and form stress cracks, which breaks the continuity of the coating. This may result in the loss of CR properties.\textsuperscript{127} High air-flow rates may also increase the spray-drying effects as discussed in the previous section.

1.9.3. Atomizing Air Pressure

Pneumatic nozzles are commonly used for spray coating of multiparticulates. These nozzles make use of atomizing air pressure to shear the coating materials into fine atomized droplets. Higher atomizing air pressure results in smaller spray droplets.\textsuperscript{128} When the atomizing pressure is too high, spray droplets may be so small that complete or partial spray drying occurs before they reach the core surfaces. The spray-dried particles hinder coalescence when embedded within the coats. High atomizing air pressure also increases
the attrition of cores during fluidization, producing more fines. On the other hand, low atomizing pressure produces larger spray droplets, which may form liquid bridges between the cores, leading to increased agglomeration rates.\textsuperscript{112}

1.9.4. **Coating Material Spray Rate**

High spray rates increase the propensity for agglomeration and form less uniform coats, while low spray rates increase the coating uniformity.\textsuperscript{82} However, when spray rates are too low, fewer spray droplets are deposited on the surface. These have a higher tendency to dry before coalescing, resulting in poorly formed coats.\textsuperscript{112}

1.9.5. **Curing Conditions Temperature**

After coating, the particles are cured to allow further water evaporation and coalescence of polymer particles. This process has been found to improve the coalescence and mechanical strength of coats.\textsuperscript{54} Curing may be done by placing the coated particles in a ventilated oven at a predetermined temperature for certain duration. Higher temperatures and longer duration are required for polymers with a higher glass transition temperature.\textsuperscript{22} Generally, the curing temperature must exceed the minimum film-formation temperature but should not exceed the glass transition temperature of the polymer. Beyond the glass transition temperature, the polymer coat would become soft and sticky, leading to agglomeration.\textsuperscript{129} The duration of curing may be selected as that beyond which there is no further coalescence. Gilligan and Po\textsuperscript{139} found that curing of ethylcellulose-coated pellets at 60\textdegree C for at least 1 hour was necessary to prevent changes in drug release during storage and increased curing duration improved the CR effect.
1.10. Objectives of the Study

Drug pellet/particle/granule coating is a big challenge and is not as easy as conventional coating of tablets because of their small size, low density and large surface area. The case with which pellets can be coated depend upon –

1. Coating composition employed viz. organic solutions, aqueous dispersions or hot-melt system.

2. Coating technology employed to coat the drug pellets viz. coating pan, centrifugal granulator (tangential-spray coater), fluid-bed devices, etc.

The aim of the present study was to evaluate the various coating formulation strategies and coating technology for preparation of coated drug pellets (having the desired characteristics) in the production of multiparticulate formulations, using certain model drugs.

1.11. Plan of Work

The plan of work was as follows –

1. Comparison of pellet coating efficiency of Wurster coater, tangential spray coater and modified coating pan using aspirin as the model drug.

2. Comparison of organic and aqueous coating compositions for pellet coating in the preparation of delayed-release rabeprazole sodium pellets.

3. Comparison of taste-masking efficiency of Eudragit polymers in the preparation of ciprofloxacin hydrochloride pellets.

4. Evaluation of cellulose and acrylic polymers in the design of controlled-release propranolol hydrochloride pellets.