1. INTRODUCTION

1.1 Drug Delivery Systems

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. Drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug [1]. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. If a device is introduced into the human body for purposes other than drug administration, such as therapeutic effect by a physical modality or a drug may be incorporated into the device for preventing complications resulting from the device, it is regulated strictly as a device. There is a wide spectrum between drugs and devices, and the allocation to one or the other category is decided on a case by case basis. Delivery of the drugs can be achieved using various types of dosage forms including tablets, capsules, creams, ointments, liquids, aerosols, injections, and suppositories [2].

Oral administration is the predominant route of drug delivery. More than 50% of DDS available in the market are meant for oral administration. These dosage forms are easy to administer and increase the patient compliance. However, the development process of such systems is precluded by several physiological difficulties. Orally administered dosage forms are exposed to a wide range of highly variable conditions during their transit throughout the gastrointestinal tract like, food ingestion, type of meal, caloric content volume, viscosity and physical state influence the gastric physiology and thus affecting the dissolution of the active drug from dosage forms (DFs) [3].

Most of these conventional drug delivery systems are known to provide immediate release of the drug with little or no control over delivery rate. To achieve and maintain therapeutically effective plasma concentrations, several doses are needed daily, which may cause significant fluctuations in plasma level concentration. Due to these
fluctuations in drug plasma levels, the drug level could fall below the minimum effective concentration (MEC) or exceed the maximum tolerable concentration (MTC). Such fluctuations result in unwanted side effects or lack of intended therapeutic benefit to the patient.

To overcome these limitations of conventional DDS, sustained-release and controlled-release drug delivery systems have been used which deliver the drug over a period of time and can reduce the undesired fluctuations of drug levels thus diminishing side effects while improving the therapeutic outcome of the drug. Sustained release (SR) preparations are not new but several new modifications are being introduced. They are also referred to as “long acting” or “delayed release” when compared to “rapid” or “conventional” release preparations. The term sometimes overlaps with “controlled release,” which implies more sophisticated control of release and not just confined to the time dimension.

Figure 1: Immediate versus controlled release drug delivery system

Lag time in pharmacokinetics corresponds to the finite time taken for a drug to appear in systemic circulation following extravascular administration is one of the limitations of these DDS. Lag time is a reflection of the processes associated with the absorption phase such as drug dissolution and/or release from the delivery system and drug migration to the absorbing surface [4].
1.2. Biphasic Drug Delivery System

Generally, conventional sustained/controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. While immediate release tablets release the drug at a faster rate to provide rapid onset of action, however it fails to provide longer duration of action. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they can either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides release vice versa [5,6]. Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents. On the basis of these considerations, we have proposed a new oral delivery device, in the form of multiple unit dosage form enclosed in to the capsule, in which the one portion is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time [7]. The second portion
is a prolonged-release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipients powder that fills the void spaces between the mini-tablets incorporate a part of the total drug dose. This system can produce a rapid rise in the plasmatic concentrations for some drugs (such as analgesic, anti-inflammatory, antihypertensive and antihistaminic agents) that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations. The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules.

Figure 3: Ideal plasma concentration curves for immediate release, zero order release, sustained release drug delivery system

1.3. Solid Dispersion

Oral bioavailability of drugs depends on its solubility and/or dissolution rate. The major problem associated with class II drugs is its very low solubility in biological fluids, which results into poor bioavailability after oral administration [8-12]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble [13, 14]. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that
potential therapeutic benefits of these active molecules can be realized [15]. Therefore lot of efforts have been made to increase the dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption[16]. Therefore, pharmaceutical researchers focuses on two areas for improving the oral bioavailability of drugs include: (a) enhancing solubility and dissolution rate of poorly water-soluble drugs and (b) enhancing permeability of poorly permeable drugs[17]. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960 [18]. Solid dispersion formulation contain a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature [19]. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinyl pyrrolidone (PVPs), Gelucire 44/14, Labrasol sugars, and urea [20-22]. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique. This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability. Despite an active research interest, the number of marketed products arising from this approach is really disappointing. Only few commercial products were marketed during the last four decades [23,24].

1.4. Multiparticulate Drug Delivery System

Oral controlled release drug delivery systems are broadly classified into two types;

1) Single unit dosage forms (SUDFs) such as tablets and capsules.
2) Multiple unit dosage forms (MUDFs) such as granules, pellets and mini tablets.
INTRODUCTION

The concept of the multiple unit dosage form was initially introduced in the early 1950s. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. [25].

Multiunit particulate systems (MUPS) are a novel MDSS technique for controlled and modified drug delivery. MUPS offer various advantages over other systems, including reduced risk of local irritation and toxicity, predictable bioavailability, reduced likelihood of dose dumping, minimized fluctuations in plasma concentration of drug, and high dose-strength administration. Multiparticulate systems show more reproducible pharmacokinetic behaviour and lower intra- and inter subject variability than conventional (i.e., monolithic) formulations and tableting of pellets reduces the esophageal residence time, compared with capsules, and improves physicochemical stability, compared with suspensions. The applications for which MUPS formulations are developed include taste masking (i.e., orodispensible MUPS tablets), enteric release (e.g., of acid-labile drugs), and modified- or controlled release orodispensible drugs for geriatric or pediatric patients. [26].

In the treatment of some diseases, polypharmacy is always applied but by designing a drug delivery system that has the entire various active pharmaceutical ingredients in one capsule can be always beneficial which deliver the drug at right time and in proper amount according to body’s circadian rhythm. According to recent pharmaceutical applications involving pulsatile delivery of the multiparticulate dosage forms are getting much favor over single unit dosage form due to their smaller particle size which can pass through the GI tract easily, leading to less inter as well as intra subject variability [27].

Recent trends specify that multiparticulate drug delivery systems are specifically suitable for achieving controlled or delayed release oral formulations with smallest amount risk of dose dumping, flexibility of combination to achieve different release patterns with reproducible and little gastric residence time. The drug release pattern from these systems depends on a carrier which is used in the formation of multiparticulates and the amount of drug enclosed in them. Thus multiparticulate drug
delivery systems provide incredible opportunities for designing novel controlled and delayed release oral formulations. The oral route is most frequently used route for oral administration of drugs. A tablet forms considerably the majority of oral dosage form due to their convenience of application and ease of preparation on an industrial scale. A major percentage of active pharmaceutical ingredients predicted through discovery screening programs are poorly soluble in water. These molecules are complex to formulate using conventional approaches and are linked with immeasurable formulation-related performance issues: poor oral bioavailability; lack of dose proportionality; and slow onset of action. Using the conventional dosage form, drugs are on occasion unable to achieve steady-state plasma concentrations so the difficulty of over or under medication may take place. The risk of adverse effects due to poor patient compliance rises. These challenges can be minimized by the use of controlled drug delivery systems that give several benefits, like the drug being delivered at a programmed rate for exact period of time and at definite site, reduced frequency of administration, reduced side effects with enhanced patient compliance, amplified safety margin of highly potent drugs, lowered healthcare costs, and enhanced therapy.

The basic concept of multiple-unit systems is that the dose of the active ingredient is released by the individual subunits like pellets, and the functionality of the entire dose depends on the quality of the subunits. The idea behind designing multiparticulate dosage forms is to build up a reliable formulation which has all the advantages of single unit formulations without danger of modification in drug release profile and formulation behavior owing to unit to unit variation [28]. These delivery systems are mainly reservoir type of oral dosage forms having multiplicity of small distinct units, each having some preferred characteristics. In these types of drug delivery systems, the dosage of the drug substances is separated on a plurality of subunit. Multiparticulate dosage form is pharmaceutical formulations where the active substance is in the form of number of small independent subunit [29, 30].

The formulation of MUDFs is a common strategy to control the release of a drug as shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFs. Among the various types of multiple unit dosage forms, pellets and mini tablets have been attracted more attention due to their unique clinical and technical advantages [31].
1.4.1. Pellets

Traditionally, the word „pellets“ has been used to describe a variety of systematically produced geometrically defined agglomerates obtained from diverse starting materials using different processing condition. Pelletization is an agglomeration process that converts fine powders or granules of bulk drug and excipients into small, free flowing, spherical or semi spherical units referred to as pellets. These pellets usually range in size from 0.5-1.5mm [32, 33].

**Advantages of pellets**

- Pellets disperse freely in the gastrointestinal (GI) tract, and so they invariably maximize drug absorption, reduce peak plasma fluctuation [34] and minimize potential side effects without appreciably lowering the drug bioavailability.
- Pellets also reduce variations in gastric emptying rates and overall transit times. Thus inter- and intra-subject variability of plasma profiles, which is common with single unit regimens, is minimized.
- High local concentration of bioactive agents, which may inherently be irritative or anesthetic, can be avoided.
- When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping [35], than the reservoir-type, single unit formulations.
- Better flow properties, narrow particle size distribution, less friable dosage form and uniform packing.
- Pellets also offer the advantage of flexibility for further modifications such as compression to form tablets or coating; achieve the desired dosage-form characteristics.

1.4.1.1. Methods of pellet preparation

Pellets are spheres of varying diameter and they may be prepared by using different methods according to the application and the choice of producer. They are

- Spray-drying
- Spray congealing
- Fluidized bed technology
Rotary processor
Extrusion and Spheronization

Of all the above methods, extrusion and spheronization is the most preferred method of pellet preparation and was used in this study.

**Extrusion and spheronization**

Extrusion and spheronization is currently one of the techniques used to produce pharmaceutical pellets. With each production technique, pellets with specific characteristics are obtained. The preparation of spherical granules or pellets by extrusion and spheronization is now a more established method because of its advantages over the other methods [36,37].

**Advantages of the extrusion and spheronization process** [38]

- Ease of operation
- High throughput with low wastage
- Narrower particle size distribution
- Production of pellets with low friability
- Production of pellets that are suited for film coating
- More sustained and better controlled drug-release profile when compared with other techniques

**Process and equipment**

In basic terms, the extrusion and spheronization process involves four steps:

- Granulation - preparation of the wet mass;
- Extrusion - shaping the wet mass into cylinders;
- Spheronization - breaking up the extrudates and rounding off the particles into spheres;
- Drying - drying of the pellets
1.4.1.2. Theory of pellet formation and growth

In order to judiciously select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanism of granule formation and growth. Results obtained from experiments with some form of tracer techniques are regarded as acceptable and convincing. In the classical pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: namely nucleation, transition and ball growth [39].

It is important to understand the fundamental mechanisms of pellet formation and growth for proceeding to the further selection and optimization of any Pelletization/Granulation process. Different theories have been postulated to explain the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing classification of pelletization process, involves three consecutive regions [40].

1. Nucleation.
2. Transition.
3. Ball growth.

However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed for pelletization:

1. Nucleation.
2. Coalescence.
3. Layering.
4. Abrasion transfer.

Nucleation is an initial stage of pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form threephase (air-water-liquid nuclei) system which are held together by liquid bridges with a pendular nature. The smaller particle size will improve the bonding strength between them. Further the size, rate and extent of nuclear formation depends upon the size of the particles, moisture content, viscosity of the binding particles, wettability of the substrate and the processing conditions, such as tumbling and drying rates. Nucleation is followed by a Transition phase where the growth mechanisms affecting are coalescence and layering.

Coalescence is formation of large-sized particles by random collision of well-formed nuclei, this mechanism require slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced with the increase in the moisture. However the total mass of the system remains unchanged during this operation.

Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei. In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time. The fragments or fine particles can be obtained with the particle size reduction. During the process these fines and the fragments produced through size reduction are taken up by larger pellets. This can be seen in the Figure 5
Production of fines and subsequent coalescence and layering continues until the number of 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 [41].

The main mechanism in this ball growth phase includes the Abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in direction. This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist.

1.4.1.3. Pellet formulation

This multiple unit dosage form technology has the potential for delivery of variety of APIs. The different drugs can be used to develop immediate release, sustained release pellets with diversified applications in different areas. Pellets can be formulated with the drugs that can be delivered even subcutaneously and intramuscularly depending on the size variations where the size range is maintained below 600 microns and are called as micropellets. Pellets technology is widely used to deliver GIT drugs at a specific site to release drug in a controlled manner.
**Binder**

They are also called as agglomerating inducers or bridging agents. These are adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation and the addition of the binder may be as a solution, than the dry form, which is considered to be more efficient than dry mixing followed by liquid addition. When applied as solution form, binders are dissolved/dispersed in organic or aqueous solvent; the latter is most preferred and commonly used system in pelletization. Choice of binders may differ from formulation to formulation and depends on the processing and physicochemical properties of the drug. The mechanism of action of the binder involves formation of liquid bridge that holds the particles together; but as the liquid evaporates the precipitation and hardening of binder takes place leading to main bonding force and with a possibility of the soluble constituents to crystallize and contribute to the bonding mechanisms. The binders are commonly used in the range of 2-10%w/w or v/v and should be optimized so that the pellets are durable and not friable and yet to maintain the other desirable properties of the pellets, such as releasing the drug at the intended rate [42].

**Granulating fluid**

Moisture content of the wet mass prepared is the most crucial parameter for pellet growth as it imparts the required plasticity and cohesiveness to the wet mass to extrude it and spheronize it to give a perfect spherical shape. An optimum quantity of moisture content should be there to obtain a good quality pellet [43]. The presence of excess moisture content leads to agglomeration of pellets during the preparation process due to the presence of excess solvent system on the surface of pellets while less quantity leads to generation of fines with large size distribution of pellets.

Different types of granulating fluid are used for the pelletization process. Besides the use of aqueous forms as a granulation liquid, use of alcoholic or hydroalcoholic systems, ethyl ether, dilute acetic acid, isopropyl alcohol has also been reported. The minimum of 5% of granulation liquid had to be water in order to produce pellets containing Avicel PH 101 and theophylline (90:10 w/w). He used water and dilute acetic acid in different powder to liquid ratios in order to increase the mass fraction of...
chitosan within the pellets and concluded that mass fraction can be increased to 100% by using dilute acetic acid for granulation step in place of demineralized water [44]. Binders are usually not incorporated, as the addition of binders [Micro Crystalline Cellulose (MCC)] provides more cohesiveness. However, researchers have attempted to incorporate various binders in the moistening liquid [45].

**Spheronising enhancer**

Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity.

**Filler**

These are the excipients used to form the bulk of the material, in the process of pelletization, 70 to 80% of the excipients is formed by fillers. Generally microcrystalline cellulose is used for this purpose. Avicel PH 101 is considered to be the pelletization aiding excipient in this process. The examples of filler i.e. Glyceryl mono stearate, Starch RX1500, spray dried lactose [46].

**Plasticizer**

Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. Sometimes drugs and other excipients are employed as plasticizers. Reported that non-traditional plasticizers including methyl paraben and drugs such as ibuprofen were able to lower the glass transition temperature of polymeric films prepared from aqueous latex dispersion of Eudragit RS 30 D [47]. The plasticizer selection will depend upon its compatibility with the polymer and also solvent employed in the casting of strip. These excipients used in hot melt extrusion method affect the release behavior of the drug. The flow of polymer will be improved with the use of plasticizer that enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives
such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients.

**Lubricant**

In pelletization process, lubricants are rarely used as the high-speed rotary equipments are being used in the preparation of pellets. However, during compression and Extrusion-Spheronization, lubricants do play a crucial role in the successful manufacture of pellets. Their use reduces the friction between the die wall and material mix either during the compression process or in ejection phase. They also play a significant role in smooth discharge of the pellets from the Spheronizer [48].

**Separating agents**

Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process, binding the pellets together leads to the formation of aggregates due to subsequent addition of binding agents, and agglomeration of pellets due to the wetness of the surface of the pellets coupled with the local concentration of the binding agents. The amount of separating agent used differs with the type of formulation and the manufacturing process and they are used in dry form during spheronization to prevent adhesion of the spheres to the friction plate and the cylindrical wall of the Spheronizer.

**Release modifiers**

The main requirement of pelletization process is to manufacture spherical drug cores that will be subsequently coated in a separate unit operation. It is also possible to prepare pellet cores that inherently possess specific release profiles in a single step which can be achieved by the incorporation of release modifiers along with drug during the core formulation. Due to the diversity of chemical composition and physical properties of release modifiers, pellet formulations that provide a multitude of release profiles could be designed. Generally, water soluble low molecular weight...
Excipients, surfactants and disintegrants are incorporated in formulations to enhance the drug release kinetics, while water insoluble polymers, hydrophobic substances, inorganic salts, and hydrophilic polymers that swell and/or form gels are incorporated in pellets that retard release kinetics [49].

1.4.2. Mini Tablets

Mini tablets (MTs) are small tablets with a diameter typically equal to (or) less than 3mm that are typically filled into a capsule or occasionally further compressed into larger tablets. It is possible to incorporate many different mini tablets each one formulated individually and programmed to release drug at different sites within the gastrointestinal tract, into one capsule. These combinations may include immediate release, delayed release and/or controlled release MTs [50, 51].

The production of mini matrices using tabletting technique is an attractive alternative to the production of pellets, as the presence of solvents (e.g., water) is avoided and high production yields like the ones observed in extrusion and spheronization are obtained [52]. Furthermore, due to the manufacturing process, defined size and strengths can easily be produced with small variability within and between batches. When mini tablets are compacted into bigger tablets because of their size uniformity, regular shape, smooth surface, low porosity and high attainable strength, it can maintain their structure and shape in a more reproducible way than usual pellets or granules, once they are compressed into a tablet system [53].

The development of mini matrices is a promising area concerned with a high control over the release rate of the drug combined with a high flexibility on the adjustment of the dose and the release of a drug or drug/s. It is characterized by the fact that the dose is administered as a number of subunits. Each one containing the drug, the dose is the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits.

Advantages

- Mini tablets mostly having a diameter of 2-3mm can be manufactured with higher reproducibility compared to pellets, especially regarding their weight.
and equal dimensions with smooth regular surface, high strengths and low porosity.

- MTs are less dependent on gastric emptying resulting in less inter-intra subject variation in gastrointestinal transit time. [54,55]
- These are better distributed and less likely to cause local irritation.
- MTs have fast onset of action due to higher surface area.
- A high degree of dispersion in digestive tract, less absorption variability and a lesser risk of dose dumping.
- Hydrophilic mini matrix tablets encapsulated into hard gelatin capsules have distinct advantages over single unit dosage forms (SUDFs) like uniform plasma levels and reproducible bioavailability.
- The tabletting behavior of tabletting mixtures using small diameters seems to provide advantages. A patent of Nordmark company points out that they were able to produce mini tablets but not 10mm tablets with a content of 99.5% Pancreatin. The study found out mixtures not able to form normalized tablets could be tabletted to mini tablets of sufficient physical quality.

1.4.2.1. Theory of mini matrix system

In order to delay the drug release corresponding to the prolonged release component of dual release system, EC and HPMC are used as matricial agents to control release of the drug from the mini tablets. In matricial systems, the characteristics of the matrix forming agent play an important role in the release mechanism of the drugs. Among the hydrophilic polymers, HPMC is one of the most commonly used carriers for the preparation of oral controlled drug delivery systems due to its ability to swell upon jellification, once in contact with water. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and efflux of the drug in solution [56, 57].

On the other hand, hydrophobic can be alternatives to the swelling polymers by forming an inert matrix with no physiological action and stable at different pH values and moisture levels. When a tablet with a hydrophobic polymer is placed in the dissolution medium, the drug at the surface is released quickly with a possible burst effect, requiring its replacement by drug from inner layers that must diffuse through the pores until it reaches the surface. When hydrophilic polymers come into contact with liquid
hydrate, a gel layer is formed. The formation of the gel layer is essential for sustaining and controlling drug release from polymer solid dosage forms. The thickness of this hydrated layer determines the diffusion of drug molecules through the polymer mass into the liquid medium, but diffusion is not the only mechanism controlling drug release. The rate and extent of drug release also depends on the swelling and erosion of the hydrated polymer preparation. Controlled drug delivery from water swellable matrix systems (hydrogels) has been used in pharmaceutical industry for more than 40 years. In the case of oral controlled release dosage forms, the most commonly used hydrophilic carrier material is HPMC, which has been used since the early 1960s. It displays good compression characteristics, has adequate swelling properties (i.e., degree and timing of swelling), can accommodate high levels of drug loading and is considered non-toxic [58].

However, the underlying mechanisms of drug release from these systems are complex, involving up to three moving boundaries usually termed the swelling, diffusion and erosion fronts. The physical process that arises when a drug loaded swellable high viscosity HPMC matrix is exposed to radial water uptake [59]. Three distinct moving fronts are present in matrix. The innermost is the swelling front, which represents the boundary between the still glassy polymer (zone 1) and its rubbery (or gel) phase (2 or 3). The HPMC present in the zone is in the glassy (crystalline) because water has not yet penetrated and subsequently plasticized the matrix by reducing the glass transition temperature from somewhere between 154 & 184°C to below the system temperature (37°C) [60].

In zone 1, the mobility of the macromolecules is very low diffusion rates of water (of the order of $10^{-16}$ m/s at 37°C). According to Fyfe and Blazek, the swelling of the HPMC matrix can be attributed to the disruption of hydrogen bondings among the polymer chains. When water penetrates the solid HPMC, it inserts itself into the hydrogen bonds between adjacent polymer chains, the forces between the chains diminish. The chains initially gain rotational freedom and begin to occupy more space, which results in the swelling of the polymer. The penetrating water fills the voids between the polymer chains apart. In zone 2 and 3 the mobility of the polymer chains is marked by increased compared to the situation in zone 1 leading to much higher diffusion rates of water (of the order of $10^{-10}$ m/s at 23°C). The drug
diffusion front consists of the boundary between solid (zone 2) and dissolved drug (zone 3). Hence, drug dissolution takes place at this very front and dissolved drug subsequently diffuses in the radial direction towards the erosion front. The latter is simply the boundary between the matrix surface and the dissolution medium [61].

**Figure 6:** Schematic illustrations (cross-section view) of a swellable HPMC-based matrix tablet during radial drug release.

The three distinct moving fronts are indicated on the figure. At all times the dissolved drug profile extends from the diffusion to the erosion front and the water profile from the swelling to the erosion front (i.e. the entire gel layer). The HPMC matrix may undergo erosion (dissolution upon prolonged contact with water). For a given HPMC matrix in a specified dissolution medium the relative movement of the fronts are determined by the matrix load and the physical properties of the drug.

### 1.4.2.2. Formulation of minitablets

MUDFs have the potentiality for delivery of variety of APIs. It is possible to incorporate many different minitablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal tract, into one capsule. These combinations may include immediate release, delayed release and/or controlled release MTs. Mini matrix dual release systems can produce a rapid rise in the plasmatic concentrations for some drugs like analgesics, anti-
inflammatory, antihypertensive and antihistaminic agents that are required to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations. This technology can be used in development of gastro retentive floating minitablets and ocular minitablets. It is also possible to incorporate minitablets of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome while delivering distinct release rates of each according to disease requirement. Minitablets could also offer a solution to current issue in the pharmaceutical industry representing a lack of dosage forms which are suitable for pediatrics.

**Diluents**

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. The dose of some drugs is sufficiently high that no filler is required. The diluent selected should be non-toxic, physiologically inert, physically and chemically stable by themselves and in combination with drug and other components. Lactose is most widely used diluents in tablet formulation. It is an excipient that has no reaction with most of the drugs, whether it is used in hydrous or anhydrous form. Spray dried lactose is one of the several diluents for direct compression. Microcrystalline cellulose often referred to by the trade name Avicel, is a direct compression material [62]. Two tablet grades exists PH101 (powder) and PH102 (granules). The flow properties of the material are generally good and the direct compression characteristics are excellent. This is somewhat unique diluents in that, while producing cohesive compacts, the material also act as a disintegrating agent.

**Binder**

A binder (also sometimes called adhesives) is added to a drug filler mixture to ensure that granules and tablets can be formed with the required mechanical strength. Binders can be added to a powder in different ways.

- As a dry powder which is mixed with other ingredients before wet agglomeration.
  During the agglomeration procedure the binder might thus dissolve partly or
completely in agglomeration liquid.

- As a solution which is used as agglomeration liquid during wet granulation. The binder here is often referred to as a solution binder.
- As a dry powder which is mixed with the other ingredients before compaction. The binder here is often referred to as a dry binder.

Both solution binders and dry binders are included in the formulation at relatively low concentrations, typically 2-10% by weight. Common traditionally solution binders are starch, sucrose and gelatin. More commonly used today with improved adhesive properties are polymers such as polyvinyl pyrrolidine and cellulose derivatives (in particular HPMC). Important examples of dry binders are MCC and cross linked PVP.

**Glidant**

The role of the glidant is to improve the flowability of the powder. This is especially important during tablet production at high production speeds and during direct compaction. However, because the requirement for adequate flow is high, a glidant is often also added to granulation before tabletting. Traditionally, talc has been used as a glidant in tablet formulations in concentrations of about 1-2% by weight. Today the most commonly used glidant is probably colloidal silica which is added in very low proportions (about 0.2% by weight) because the silica particles are very small, they adhere to particle surfaces of the other ingredients and improve flow by reducing interparticulate friction.

1.4.2.3. Granulation methods

**Wet granulation**

The most widely used and most general method of tablet preparation is the wet granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for compression of good tablet. Its chief disadvantages are the number of separate steps involved as well as the time and labor necessary to carry out the procedure, especially on a large scale.

The steps in the wet method are weighing, mixing, granulation, screening the
damp mass, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluents and disintegrants are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars.

The powder blend may be sifted through a screen of suitable fines to remove or break up lumps. This screening also affords additional mixing. The screen selected always should be of same type, of wire or cloth, that will not affect the potency of ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper containing alloys.

Solutions of the binding agents are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow. If the granulation is over wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently granules will be too soft, breaking down during lubrication and causing difficulty during compression. The wet granulation is forced through a 6 or 8 mesh screen. Small batches can be forced through hand using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used.

Most material from the wet milling step traditionally was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. While tray drying was most widely used method of drying tablet granulations in the past, fluid bed drying is now considered the standard. The application of microwave drying and infrared drying to tablet granulations tried. In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums in a hydrated state. Also, the residual moisture contributes to the reduction of static electric charges on the particles.

In selection of any drying process an effort is made to obtain uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products...
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containing moisture sensitive active ingredients may be related to the moisture content of the products. After drying, the granulation is reduced in particle size by passing it through a smaller mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested:

- Tablets up to 3/16 inch diameter use 0 mesh.
- Tablets 7/32 to 5/16 inch use 16 mesh.
- Tablets 11/32 to 13/32 inch use 14 mesh.
- Tablets 7/16 inch and larger use 12 mesh.

After dry granulation, the lubricant is added as a fine powder. It is usually screened onto the granulation through 60 or 100 mesh nylon cloths to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation, preferably in a blender using a tumbling action.

Fluid bed granulation

A new method for granulating evolved from the fluid bed drying technology. The concept was to spray a granulating solution onto the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The two main firms that developed this technology are Glatt and Aeromatic (now NIRO). In this method, particles of an inert material or the active drug are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation that is ready for compression after the addition of the lubricant. An obvious advantage exists since granulating and drying can take place in a single piece of equipment. In these systems a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the air, volume and moisture of the air, play an important role in the quality and performance of the final product. In addition to its use for the preparation of tablet granulation, this temperature also has been proposed for the coating of solid

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particles as a means of improving the flow properties of small particles

_Dry granulation_

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression or double compression. It eliminates a number of steps but still includes weighing, mixing, slugging, drying, screening, lubrication and compression. The active ingredient, diluents (if required) and part of the lubricant are blended. One of the constituents either the active ingredient or the diluent must have cohesive properties. Powdered material contains a considerable amount of air, under pressure this air is expelled, and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

When slugging is used, large tablets are made as slugs because fine powders flow better into larger cavities. Also, producing large slugs decreases the production time, 7/8 to 1 inch are the most practical sizes for slugs. Sometimes, to obtain the pressure that is desired the slug sizes are reduced to ¾ inch. The punches should be flat faced. The compressed slugs are committed through the desirable mesh screen either by hand or for larger quantities through comminuting mill. The lubricant remaining is added to the granulation and blended gently and the material is compressed into tablets.

_Direct compression_

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as a method of manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, and permanganate), ammonium chloride and methylamine. These materials possess cohesive and flow properties that make direct compression possible.
Since the pharmaceutical industry constantly is making efforts to increase the efficiency of tabletting operations and reduce costs by using the smallest amount of floor space and labor a possible for a given operation, increasing attention being given to this method of tablet preparation. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression and the use of force feeding devices to improve the flow of powder blends. For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with suitable diluents that acts as a carrier or vehicle for the drug. Direct compression vehicles or carriers must have good flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization or crystallization. These vehicles included processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray dried lactose, pregelatinized starch, compressible sugar, mannitol and MCC. The excipient that has been studied extensively as a direct compression vehicle is MCC (Avicel). This non fibrous form of cellulose is obtained by spray drying wash, acid treated cellulose and is available in several grades that ranges average particle size from 20 to 100µm. It is water insoluble, but the material has the ability to draw fluid into a tablet by capillary action, it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self lubricating qualities thus requiring a lower level of lubricant than other excipients.

By considering the merits of multiparticulate drug delivery systems, an attempt was made to formulate a dual release drug delivery system consisting of solid dispersion with either pellets or minitablets in order to enhance the bioavailability and to possess the advantages of both immediate release and sustained release delivery systems using BCS Class II drug as a model agent.