ABSTRACT
Recently, extended release pharmaceutical products became a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which lead to better patient compliance. So, oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. Extended release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Oral extended release drug delivery medication will continue to account for the largest share of drug delivery systems. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving extended release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from pellets depends on a variety of factors including the carrier used to form pellets and the amount of drug contained in them. Consequently, pellets provide tremendous opportunities for designing new controlled and extended release oral formulations, thus extending the frontier of future pharmaceutical development.

KEYWORDS: Extended Release, Oral route, Therapeutic concentration, Pellet, Dosage form.

INTRODUCTION
The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more
flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.\textsuperscript{[1,2]}

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.\textsuperscript{[2]}

**Drawbacks of Conventional Dosage Form.\textsuperscript{[3]}**

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

**Advantages of Extended Release Delivery System.\textsuperscript{[4]}**

- The extended release formulations reduce dosing frequency of drugs.
- The extended release formulations may maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of these formulations avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes
in gastrointestinal tract.

- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.
- Improve the ability to provide special effects.
  
  For example, Morning relief of arthritis through bed time dosing.

**Disadvantages of Extended Release Delivery System.**[4]

- Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- The larger size of extended release products may cause difficulties in ingestion or transit through gut.
- The release rates are affected by various factors such as food and the rate of transit through the gut.
- Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- High cost of preparation.
- Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

**Rationale of Extended Drug Delivery.**[5]

The main objective to formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favourable. This change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameters.

![Figure 1: Plasma Concentrations](image)

**Pellets**

Pelletization is an agglomeration process, that converts fine powder blend of drug(s) and excipients into small, free flowing, spherical units, referred to as pellets.
Rationale of extended release pellets

Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and can also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.\(^6\)

Advantages of extended release pellets

- Reduce dosing frequency of drugs.
- Maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of pellets avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.
- Improve the ability to provide special effects.

DRUG PROPERTIES OF EXTENDED RELEASE FORMULATIONS

During design of extended release delivery systems, variables such as the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. These properties are classified as:

(a) Physicochemical

(b) Biological properties

These properties have the greatest effect on the behaviour of the drug in the delivery system and in the body. There is no clear cut distinction between these two categories since the biological properties of a drug are a function of its physicochemical properties. By definition, physicochemical properties are those that can be deter-mined from in vitro experiments and biological properties will be those that result from typical Pharmacokinetic studies of the absorption, distribution, metabolism, and excretion (ADME) characteristics of a drug and those
resulting from pharmacological studies.[7]

**Physicochemical Properties**

a) Dose Size  
b) Aqueous Solubility and pKa  
c) Partition Coefficient  
d) Drug Stability  
e) Molecular Size and Diffusivity  
f) Drug Protein Binding

**Biological Properties**

a) Absorption  
b) Distribution  
c) Metabolism  
d) Elimination and Biological Half-Life

**Approaches to Achieve Extended Release Drug Delivery**

The purpose of designing ER dosage form is to develop a reliable formulation that has all the advantages of immediate release dosage form and yet devoid of the dose dumping. Various techniques have been used in the formulation of ER products. In general, extended formulations can be divided into different categories based on the mechanism of drug release.[8, 9]

1) Dissolution Controlled Release  
2) Diffusion Controlled Release  
3) Ion Exchange Resins Controlled Release  
4) Swelling Controlled Release.

**Dissolution Controlled Release**

This type of controlled release involves two processes, the detachment of drug molecules from the surface of their solid structure to the adjacent liquid interface, followed by their diffusion from the interface into the bulk liquid medium. The rate of dissolution and the amount dissolved per unit of time from this system can be calculated using Noyes-Whitney equation which relates the rate of dissolution of solids to the properties of the solid and the dissolution medium, and the relation is given by:

\[
\frac{dW}{dt} = DA (C_s - C)
\]
dW/dt is the rate of dissolution;
A is the surface area of the solidification;
C is the concentration of the solid in the bulk dissolution medium;
Cs is the concentration of solid in the diffusion layer surrounding the solid;
D is the diffusion coefficient and
L is the diffusion layer thickness.

**Diffusion Controlled Release**

In this type of controlled release system, the active ingredient diffuses through the polymeric material. These are mainly classified as reservoir and matrix systems.

**Reservoir system**

Cellulose derivatives are commonly used in the reservoir systems. It consists of a core (the reservoir) and coating membrane (the diffusion barrier). The active ingredient diffuses from the reservoir through the coating membrane.

For a reservoir system where the drug depot is surrounded by a polymeric hydrogel membrane, Fick's first law of diffusion can be used to describe drug release through the membrane.[10]

**Matrix system**

In this review article greater emphasis is given for matrix controlled release for design of extended release tablets. A matrix system consists of active and inactive ingredients that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral extended release technology and the popularity of the matrix systems can be attributed to several factors. The release from matrix type formulations is governed by Fick’s first law of diffusion.

**Ion Exchange Resins Controlled Release**

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway, and the amount of cross-linked polymer in the resin moiety governs the rate of drug release.

**Swelling Controlled Release**
Swelling controlled systems are based upon swelling of ER polymer. Due to the viscoelastic properties of the polymers, which are enhanced by the presence of cross-linked network, anomalous penetrate transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrate concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.[11]
Drug release from swellable matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the Primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation.

**Advantages of Matrix System**

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipments. Secondly, development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

**Limitations of Matrix System**

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix based technologies such as layered tablets are required.

**Types of Matrix System**

The matrix system can be divided into two categories depending on the types of retarding agents or polymeric materials.

1) Hydrophobic matrix system

2) Hydrophilic matrix system

**Hydrophobic Matrix System**,\(^{[12, 13]}\)

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be
necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism, and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic.

The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery have become more important. Constant rate delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index.

**Hydrophilic matrix system**

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path. It has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release.[14]

For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms.[15]
TYPES OF MULTIPARICULATE SYSTEM

A) Matrix Systems
In matrix systems a polymer: drug solution or dispersion is granulated with excipients to form pellets or sprayed onto pellets in order to achieve extended drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed or dissolved and dispersed. These systems present several advantages as follows

- Easy manufacture and low cost (1 step process),
- Lower risk of dose dumping (if the coating accidentally ruptures) and the
- Possibility of improvement of aqueous drug solubility.

Drug–polymer interactions can occur and bring benefits in terms of mechanical properties such plasticizing effect. The main disadvantages include fast initial release and incomplete release in a defined time. The latter could be avoided by coating sugar cores with different polymer: drug ratios, in which the drug was more concentrated in deeper layers of the matrix and so counteracting for the increased diffusion pathway. In addition, matrix systems were found suitable to control drug release of a highly soluble drug.\[16\]

Matrix solutions, matrix dispersions and drug release mechanisms
In matrix systems, the drug and polymer are dissolved or dispersed in a common solvent and upon solvent evaporation, a solid solution (drug dissolved in the polymer) or a solid dispersion (drug dispersed in the polymer) or a combination of both is obtained. If the initial drug concentration is below drug solubility in the polymer, drug is dissolved and drug release is mainly extended by drug diffusivity in the polymer.

B) Reservoir Coated Systems
A reservoir coated system consists of a drug layered core surrounded by a polymer. The major advantages of this system rely in the fact that very high drug loadings can be used and variable drug release profiles can be obtained, by just varying the type of polymeric membrane.

Aqueous coating and organic coating
Pellets can be coated with an aqueous polymeric dispersion or an organic solution in order to achieve extended drug release. Organic coatings present many disadvantages as the dependence of viscosity on molecular weight and the concentration of polymer used. In contrast, aqueous polymer dispersions are characterized by low viscosity even at high solid
contents, leading to a decrease in coating process time.[17] Organic solutions present additional disadvantages like the presence of residual solvents in the coating that can create changes in film properties, environmental pollution and explosion hazards. As a result, the use of aqueous polymeric dispersions is preferred for pharmaceutical coatings. However, film formation mechanisms (aqueous versus organic) are very different. With organic polymer solutions, polymer macromolecules are dissolved and this can create a high viscosity solution. During solvent evaporation, an intermediate gel-like phase is formed. After complete solvent evaporation, a polymeric film is obtained. In contrast, film formation from aqueous dispersions is a more complex process.[16] During drying of aqueous dispersions, polymer particles come into contact with each other in a closed packed order. The high interfacial surface tension between air and water leads to the formation of a layer of polymer spheres filled with water. The particle fusion or coalescence is then possible when the capillarity forces (air water interfacial tension) are strong enough. Usually the coating process is performed at sufficient high temperatures to guarantee softness of the discrete polymer particles. The softening is related to the glass transition temperature (Tg) of the polymer. A curing step (post coating thermal treatment) is carried out after coating process to assure complete film formation and avoid further gradual coalescence. The aqueous dispersions can have additional ingredients as surfactants that act as stabilizers during the production process. Other compounds as plasticizers and anti-taking agents are used to enhance the coating process and film properties. Plasticizers are added to promote the polymer particle coalescence, softening the particles and reducing minimum film formation temperature (MFT). Film formation is related to glass transition temperature of the polymer or minimum film formation of the aqueous dispersion. The MFT is the minimum temperature above a continuous film is formed during drying under standardized conditions. Below this temperature the dry latex is opaque and powdery; however these conditions are different from drying during coating.

Actually, water can decrease Tg of the some polymers (due to its plasticizing effect) and in this case the MFT is lower than the Tg of the polymer. Tg and MFT shows a linear relationship between different polymer/plasticizer concentrations.[18]
Figure 2 Spheronization Process

Figure 3 Extrusion Spheronization Technique
Drug release mechanisms

The mechanism controlling drug release from reservoir coated pellets is often a complex process and it depends on coating type and thickness, drug type and core type. One of the mechanisms is diffusion through the continuous polymer film surrounding the drug loaded core. Firstly, water penetrates through the coating until reaches the pellet core. Afterwards, drug is dissolved and released. The drug is released due to the concentration gradient inside the pellet (Ci) versus outside the pellet. In the case of perfect sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as follows (according to Fick’s law of diffusion):

\[
\frac{dM}{dt} = Dm \cdot A \cdot K \cdot \frac{C_i}{d}
\]
Dm is the apparent diffusion coefficient of the drug in the polymeric film, A the surface available for diffusion, K the partition coefficient of the drug (aqueous phase – polymeric phase), and d denotes the thickness of the film coating [20]. Unfortunately, Fick’s Law (which was only ever intended to describe diffusion in binary mixtures) cannot be extended to drug release from reservoir pellets that easily. The diffusivity for example is assumed to be constant in homogeneous, intact polymer films. However, in reality many polymers swell upon contact with medium which is known to gradually increase the diffusivity over time. In addition most polymers contain crystalline regions in which drug diffusion is negligible.

Drug diffusion in the amorphous regions of polymers has been described by the so-called ‘jump-and-run’-model. It was proposed that the amorphous segments in polymers contain homogeneous, semi-crystalline structures of polymer molecules which are aligned in parallel. Permeates like the diffusing drug ‘run’ along the tube between parallel polymer chains until reaching a ‘dead-end’ (a crystalline region or a point of high chain entanglement). There they are forced to ‘jump’ from one tube to the next, pushing and bending the polymer chains apart (Figure 5). Drug release can occur through water filled pores. These pores can be due to leaching of water soluble compounds into the release medium or due to cracks formed by high hydrostatic pressure generated inside these systems upon water uptake. Drug release can be described as follows:

\[
\frac{dM}{dt} = D_p A \varepsilon \frac{c_i}{\tau} \frac{d}{d}
\]

Where Dp is the diffusion coefficient of the drug in the aqueous phase present in the channels and pores, ε the volume fraction of the pores, τ the tortuosity of the channels [21]. Another possible mechanism controlling drug release from coated pellets is due to osmotic effects. For this mechanism to occur an osmotic active core should be surrounded by semi permeable membrane and a difference in osmotic pressure between the inner and outer side of the membrane.

Osmotically driven release depends on the porosity of the polymeric membrane and the osmotic pressure of the sugar core and the drug. Upon water uptake, drug is pushed out via pores in the coating. Drug release can be described as follows:

\[
\frac{dV}{dt} = A \theta \Delta \pi \frac{1}{l}
\]
Where \( \frac{dV}{dt} \) denotes the water flow, \( A \) the membrane surface area, \( l \) the membrane thickness, \( \theta \) the permeability of the polymeric membrane, and \( \Delta \pi \) the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure). The overall drug release rate from coated pellets may be governed by one of the above mechanism or a combination of them. Parameters as core and coating swelling also contributes to the drug release rate \[22\]. The type of drug can strongly affect the resulting drug release rates. Ibuprofen diffused through the coating (due to high solubility in the polymer) while chlorpheniramine maleate diffused through micro-channels in Aquacoat coated pellets, resulting from osmotic pressure developed by the core. Drug release rate can be affected by changes in surface area (during dissolution study) of the pellets. The coating level also changes the mechanism of drug release. At low coating levels, drug release occurred through pores in the coating, while at high coating levels drug release rate was extended by diffusion through the coating. Consequently the mechanism controlling drug release at higher coating levels was not just dependent on drug solubility but also on the polymer/dissolution medium partitioning coefficient of the drug.\[23\]

Drug release mechanism from ethyl cellulose coatings with pore formers was investigated by several researchers. At lower pore former (HPMC) contents, drug release occurred through osmotic pumping, but above a certain value diffusion also contributed to overall drug release. Addition of small amounts of polyvinyl alcohol polyethylene glycol graft copolymer to ethylcellulose coatings was found to control drug release from coated pellets irrespective of the drug solubility and type of core formulation. The mechanism controlling drug release was shown to be diffusion through intact polymeric membranes.

The glass transition temperature of the polymer also affects the drug release mechanism. With water soluble plasticizers, the polymer was in glassy state after plasticizer migration and drug diffused through water filled pores. With water insoluble plasticizers, the polymer was in the rubbery state and a two phase release mechanism was found. In the first phase drug was released through pores created by leaching of HPMC and in the second phase pore shrinking occurred leading to a decrease of free volume in the polymer chains.\[24\]

The type of coating technique (organic versus aqueous) was found to contribute to drug release mechanism in different ways. Drug release mechanism from coating with blends of a water-insoluble (ethylcellulose) and an enteric polymer (ethylcellulose: methacrylic acid ethylacrylate copolymer, Eudragit L) occurred by diffusion through the intact polymeric films
and/or waterfilled cracks. However, lower hydrostatic pressures were necessary to induce crack formation within aqueous coatings. Organic coatings were mechanically strong with high degree of polymer-polymer interpenetration and thus higher hydrostatic pressure was required to induce crack formation.

The polymer particle size affects the film coating structure and properties. Blends of aqueous dispersions of a water-insoluble and an enteric polymer, ethylcellulose and Hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and Eudragit L were used as coating materials to control theophylline release from matrix pellets. Drug releases were similar for both types of blends in 0.1 M HCl, but significant differences were observed in phosphate buffer pH 7.4. Eudragit L particles are smaller than HPMC particles (nano. vs. micrometer size range) and more effectively hinder the formation of a continuous and mechanically stable ethylcellulose network. Ethyl cellulose structures remaining upon HPMC leaching are mechanically stronger and drug release is extended by diffusion through the polymeric remnants. In contrast, ethylcellulose structures remaining after enteric polymer leaching at high pH are mechanically much weaker in the case of Eudragit L. Upon exposure to phosphate buffer, water-filled cracks are formed, through which the drug rapidly diffuses out.\[25\]

Marketed products of MUPS

Losec MUPS (Multiple Unit Pellet Systems), consisting of microencapsulated drug granules tableted with excipients is the second highest selling pharmaceutical drug product in Sweden in the year 2002.

Curing

After coating process and even with a product temperature 10-20°C above the MFT, complete film formation may not be achieved. Thus a short thermal treatment is required to complete polymer particle coalescence. At curing temperatures above the glass transition temperature, the mobility of the polymer chains increases and latex coalescence is accelerated. The curing step may be performed in an oven or in the fluidized bed coater immediately after the coating process. Too low curing temperatures can lead to incomplete film formation, whereas too high temperatures can lead to excessive tackiness and agglomeration of the solid dosage forms. The curing step can be performed at several temperatures or different times and in the presence of extended humidity. All these factors can potentially affect drug release rate. The slower release rates with increasing curing time were attributed to greater polymer particles coalescence.\[26\]

In another study, the curing
temperature and time were investigated. Drug release decreased with increasing temperature. At 30°C, the decrease in drug release was small and not affected by the curing time. When temperature and time of curing were increased, the resulting changes in drug release rate increased. It was suggested that at higher temperatures, more polymer molecules can overcome the energy barrier and reach a stable state, reflected by the slower release. On the contrary, at low curing temperatures, few molecules can achieve a stable state, meaning that changes in drug release are expected to occur slowly over time until the stable state is reached.

Extended humidity can be used during the curing step. The presence of humidity was more effective to complete film formation than without. Water facilitates polymer particle coalescence and it acts as plasticizer for many polymers. High content of plasticizer can minimize the curing effect; however there is a limit of plasticizer concentration to avoid problems as stickiness during coating process or forming agglomerates of pellets during curing. The curing effect on drug release can change depending on the type plasticizer and coating level. For example, drug release decreased with increasing harshness (time, temperature and relative humidity) of curing conditions, when using triethyl citrate & acetate as plasticizer.

Storage stability

Although the curing step is performed in order to complete film formation, drug release rate was reported to decrease especially under elevated humidity. This was mainly attributed to further gradual polymer coalescence, leading to denser films and decreased permeability for water and drug. Changes in drug release profiles were also observed with high glass transition temperature polymers. Faster drug release may be caused by brittle films or the formation of micro-ruptures in the film coat during storage. Thermal humidity curing was found to help to enhance coalesce of polymeric films, however presence of high levels of humidity during storage can destabilize films, originating changes in drug release rate over time.

FORMULATION METHODS

Extrusion Spheronization Process

The concept of multiparticulate dosage forms introduced in the 1950’s with the increasing use of multiparticulate extended release (CR) oral dosage forms, in recent times there has been a rise in interest in the methods of preparing these dosage forms. A method that has gained increased usage over the past few years is that of extrusion and spheronization. It has
extensively as a potential technique and also as a future method of choice for preparation of multiparticulate CR dosage forms. This is a multi-step process involving dry mixing, wet granulation, extrusion, spheronization, drying and screening. The first step is dry mixing of the drug and excipients in a suitable mixer followed by wet granulation, in which the powder is converted into a plastic mass that is easily extruded. The extruded strands transferred into a spheronizer, where they are instantaneously broken into short spherical rods on contact with the rotating friction plate and pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally, owing to gravity, the particles fall back to friction plate, and the cycles repeated until the desired sphericity achieved. Extrusion-spheronization is a multistep process involving a number of unit operations and equipment. However, the most critical part of processing equipment dictates the outcome of overall quality of pellets.\[^{30}\]

**Extrusion**

Shaping of the wet mass into long rods is called as extrusion. A variety of extruders, which differ in design features and working principles, are currently on market and can be classified as screw-fed extruder, gravity-fed extruder and ram extruder. Screw-fed extruder have screws that rotate along the horizontal axis and hence transport the materials horizontally, they may axial or radial screw extruders. The product temperature extended during extrusion by jacketed barrels. In radial extruders, the transport zone is short, and the material extruded radially through screens mounted around the horizontal axis of the screws. Gravity-fed extruders include the rotating cylinder and rotating gear extruders, which differ primarily in the design of two counter-rotating cylinders. In the rotating cylinder extruder, one of the two counter rotating cylinders is hallow and perforated, whereas the other cylinder is solid and acts as a pressure roller. In ram extruders, piston displaces and forces the materials through a die at the end. Ram extruders preferred during formulation development they designed to allow for measurement of the rheological properties of formulation. In an extrusion-spheronization process, formulation components such as filler, lubricants and pH modifiers play a critical role in producing pellets with desired attributes. The granulated mass must plastic and sufficiently cohesive and self-lubricating during extrusion. During the spheronization step, it is essential that the extrudates break at appropriate length and have sufficient surface moisture to enhance the formulation of uniform spherical pellets. Excipients play an important role during extrusion spheronization than during with other pelletization process. They facilitate extrusion and determine the sphericity of the wet pellets.
impart strength and integrity of the pellets. Microcrystalline cellulose (MCC) is the most commonly used excipient in extrusion spheronization it leads to the formation of round spheres with desirable characteristics.[31]

During spheronization, moisture entrapped in the MCC microfibrils adds plasticity to the extrudates into spherical pellets. The pellet properties can be affected by many operational variables during the extrusion stage, the spheronization stage, or the drying stage. Both drying technique and drying temperature have a considerable effect on the pellet structure and properties. The variables that affect the final pellet qualities are screen pressure, screen hole diameter, extruder type and speed, the type of friction plate, and spheronization time, speed and load. There is considerable interaction between spheronization time and spheronization load. With small and large spheronization loads, the yield of large pellets increases with longer spheronization time, an effect that is exacerbated by faster spheronization speed. Unsuitable processing parameters lead to pellet with poor qualities.

**Spheronization**

During the third phase of extrusion spheronization process the extrudates dumped on to the spinning plate of the spheroniser, call the friction plate, where the extrudate broken up into smaller cylinders with a length equal to their diameter, those plastic cylinders rounded due to frictional forces. In the spheronization process different stages are distinguished depending on the shape of the particles, i.e.; starting from a cylinder over a cylinder with rounded edges, dumbbells and elliptical particles to eventually perfect spheres. Another pellet forming mechanism might exist. In this mechanism twisting of a cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have round and flat side. Due to rotational and frictional forces involved in the spheronization process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets. The spheronization of a product usually takes 2-10 minutes. A rotational speed of friction plate in the range between 200 and 400 RPM would be satisfactory to get highly spherical pellet. This statement is in a sharp contrast with most reports indicating the use of spheronization speeds exceeding 400 RPM. This contradiction is explained by the fact that not the absolute speed is important but the speed in combination with the diameter of the friction plate. From those two parameters the plate peripheral velocity is calculated and this data should be compared instead of absolute rotational speed of the friction plate. The friction plate has a grooved surface to increase the
frictional forces. Two types of geometry of the grooves exist, cross hatch geometry where the grooves from right angles and radial geometry where a radial pattern used.\textsuperscript{[32]}

**Layering process**

Layering processes involve loading solid inert cores with drugs and/or excipients. Inert cores, placed in a suitable vessel such as a coating pan or a fluid bed, may be layered according to different methods. Some methods consist of spraying onto the cores a solution/suspension containing both drug and binding agent. Others are based on layering the drug directly in powdery form where drug loading occurs by gravity and adhesion is ensured by a liquid binder sprayed onto the cores.

The layering process is particularly suitable for production of small drug loaded units, multiples of which are placed into capsules for patient delivery. In the case of spherical inert cores such as nonpareils, the layering techniques from solution/suspensions produce homogeneous drug loaded particles, which retain an approximately spherical shape. They are therefore particularly suitable for successively film coating to build up the particle with the aim of providing a desired drug release profile.

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on performed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the liquid and dry powder, it generally requires specialized equipment. Pieces of equipment revolutionized powder layering processing as a pelletizing techniques are- tangential spray or centrifugal fluid bed granulators.

In case of tangential spray the rotating disk and fluidization air provides proper mixing. With a double wall centrifugal granulator, the process is carried out in the open and closed position. With powder layering, the inner wall is closed so that simultaneous application of liquid and powder could proceed until the pellets have reached the desired size. The inner wall is then raised, and the spheres enter the drying zone. The pellets are lifted by the fluidization air up and over the inner wall back in to forming zone. The cycle is repeated until the desired residual moisture level in the pellets is achieved. The principle of powder layering process with different steps is completely illustrated in figure 4.

**Evaluation Parameter of Extended Release Pellets**

- Morphological Properties
- Size and Shape of Pellet
Micromeritic Properties
In Vitro Dissolution
Drug Content

CONCLUSION
A number of drugs are now marketed in a variety of different extended release products. However, only those, which result in a significant reduction in dose frequency or reduction in dose related toxicity, are likely to improve therapeutic outcomes. Presence of food, gastrointestinal motility and concomitant administered or present material will influence the therapeutic response. The market for extended release drug delivery has come a long way and will continue to grow.

We Concluded that Pellets are for pharmaceutical purposes and are produced primarily for the purpose of oral extended-release dosage forms having gastro resistant or extended-release of extended release properties or the capability of site-specific drug delivery. For such purposes, coated pellets are administered in the form of hard gelatin capsules or in tablets. As drug delivery systems extended release pellets become more sophisticated, the role of pellets in the design and development of dosage forms is increasing. Formulation of drugs in multiple-unit dosage forms, such as extended release coated pellets filled in capsules or compressed into tablets, offers flexibility as to target-release properties. The safety and efficacy of the formulation is higher than that of other dosage forms.

REFERENCES
18. Lippold BC., Monells PR. Control and stability of drug release from diffusion pellets coated with the aqueous quaternary Poly methacrylate dispersion Eudragit RS 30 D,
Pharmazie; 2001; 56: 477-483.