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EXTENDED RELEASE PELLETS: *NOVEL APPROACH TO TARGETED DRUG DELIVERY SYSTEM*

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ABSTRACT

A variety of real and perceived benefits for patients, extended release pharmaceuticals have recently emerged as a highly helpful tool in medical practice. Due to its convenience, Among all drug delivery methods oral administration is a particularly often used method for various pharmacological compounds, which improves patient compliance. For medications that are taken orally yet have a short half-life and a high frequency of dosage, an oral extended-release drug delivery system represents a very promising strategy. By keeping the prescribed dose of the medicine from fluctuating in the body, extended release also offers a viable means of reducing pharmacological adverse effects. Drug delivery systems that use oral extended release drugs will keep up to dominate the market. The prolonged release solution will improve patient comfort and compliance while optimizing a drug's therapeutic impact and safety. Multiparticulate drug delivery methods are particularly well-suited for producing oral formulations with extended release that have a minimal chance of dosing off, may be blended to achieve various release patterns, and have a short and repeatable stomach residence time, according to recent developments. Several elements including the amount of medicine in the pellets and the carrier used to produce them, affect how much medication is discharged from them. In light of this, pellets provide a wealth of potential for creating novel controlled and prolonged-release oral formulations.

KEYWORDS: Extended pellets, Extrusion Spheronization Process, Lyophilization method.

INTRODUCTION

The oral route is the most widely used method of drug administration, partly because it is simple to administer and because gastrointestinal physiology allows for greater design freedom in dosage forms than most other routes. Drug delivery systems known as long-lasting release, prolonged release, improved release, extended release, or depot formulations are designed to achieve or prolong the positive effects by continuously releasing medication over a prolonged period of time after a single dose is administered.[1—2] These dose formulations are appealing for a number of reasons. increases the drug's bioavailability, decreases the frequency of delivery to extend the time when blood levels are effective, potentially enhances the drug's particular distribution while lowering side effects and peak-to-trough concentration fluctuations. To create the perfect medicine delivery system, two prerequisites would need to be met: The first dose is given once during the course of treatment, whether it be for days or weeks, as in the case of infections, diabetes, or hypertension. In order to minimize adverse effects, it should also deliver the active ingredient straight to the place where action takes place.

When creating prolonged release formulations, there are a few things to keep in mind: If the active ingredient has a lengthy half-life, it can last on its own. If there is no direct correlation between the active ingredient's blood levels and pharmacological activity, If active transport is involved in medication absorption and the active molecule has a short half-life, a significant amount of drug would be needed to sustain a long-lasting effective dose. Prior to design, the aforementioned elements require careful consideration.[2]

FUNDAMENTALS OF EXTENDED-RELEASE PELLETS

❖ Definition of extended release pellets

Extended-release (ER) pellets are multi-unit dosage forms that are designed to retain constant drug levels in the systemic circulation by releasing a medication at a predefined, regulated pace over an extended period of time. Usually 0.5 to 1.5 mm in diameter, these pellets are spherical particles that are created by a variety of methods, such as extrusion-spheronization, solution layering, and powder stacking. Frequently, they are compacted into tablets or placed within hard gelatin capsule.[8]

❖ **Characteristics of extended release pellets[9,10]**

CHARATERISTIC	DESCRIPTION
1. Controlled Drug Release	Designed to release drug at a specific rate to maintain therapeutic levels over an extended period.
2. Multi-Unit System	Consist of many small subunits (pellets), reducing the risk of dose dumping and improving GI tolerability.
3. Uniform Size and Shape	Typically spherical with narrow size distribution, improving flow and coating efficiency.
4. Polymer Coating	Use of polymers (e.g., ethylcellulose, Eudragit) for modifying drug release by diffusion or erosion mechanisms.
5. High Surface Area	Enhances coating efficiency and drug release control.
6. Improved Patient Compliance	Less frequent dosing due to sustained action increases adherence.
7. Flexibility in Dosage Form Design	Can combine multiple drugs with different release profiles in a single capsule.
8. Better Stability	Protects drugs from degradation (e.g., in acidic stomach)

❖ **Drawbacks of Conventional Dosage Form[3]**

- A drug with a short half-life that requires frequent administration may be missed more frequently due to poor patient compliance.
- Under- or over-medication may result from the inevitable changes in drug concentration.
- The resulting typical peak-valley plasma concentration time profile makes it challenging to achieve steady-state conditions.
- When taking too much medication, the changes in drug levels might cause negative side effects, especially if the drug has a low Therapeutic Index (TI).

❖ **Advantages of Extended Release Delivery System[4]**

- Formulations with extended release have the ability to preserve therapeutic concentrations and decrease the frequency of drug dosages.
- Slow down the absorption of drugs to lessen toxicity.
- When these formulations are used, the excessive blood concentration is avoided.
- Long-term release formulations may increase patient convenience and compliance. Cut down on systemic and local adverse effects.
- Boost stability by shielding the drug from gastrointestinal tract hydrolysis or other deteriorating processes.
- An increase in therapeutic effectiveness.
- Chronic dosage reduces the buildup of drugs.

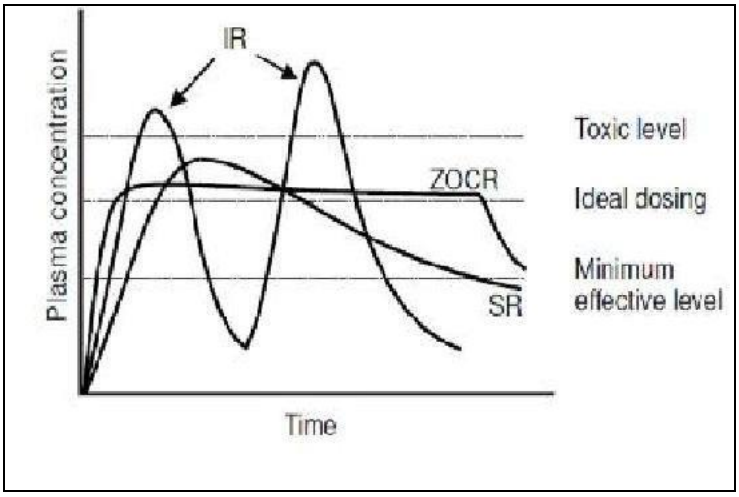
- Make some drug more bioavailable.
- Using less drug overall.
- The capacity to produce extraordinary effects should be enhanced.
- As an illustration, bedtime dosage can relieve arthritis in the morning.

❖ Drawback of Extended release delivery system[4]

- The medication load in extended-release formulations is higher, which could lead to a loss of the dosage form's release properties; also, the larger size of these items may make them more difficult to swallow or pass through the digestive tract.
- The rate of transit through the gut and the type of food have an impact on the release rates.
- The release rate varies from dose to dose, however, contemporary formulations have reduced these variations.
- The cost of preparation is high.

❖ Rationale of Extended Drug Delivery[5]

Pharmacokinetic parameters are the primary goal when formulating an API for an extended drug delivery system. Drug tolerance can occasionally occur when the target tissue is exposed to a constant dosage of the medication for a long time. However, a well-formulated product can facilitate absorption. A drug's ADME profile (distribution, metabolism, and elimination) is quite favorable. In addition to ease for patients and adherence, this modification to the ADME may have a significant effect on standards for the drug safety, effectiveness and tolerance.



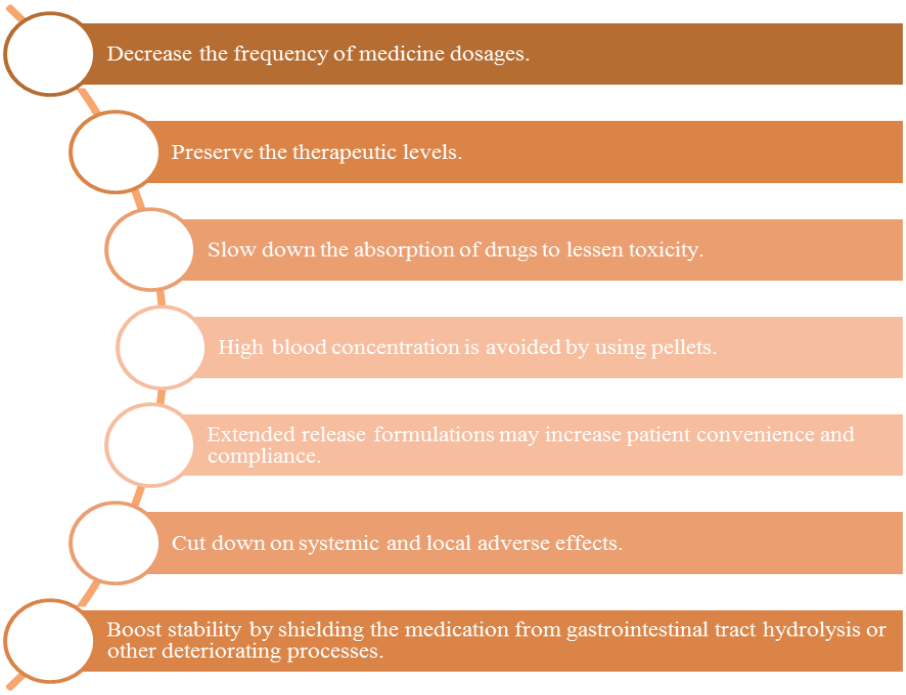
Pellets

A fine powder mixture of drug(s) and excipients is transformed into pellets, which are tiny, spherical, free-flowing particles through the agglomeration process known as pelletization.

Rationale of extended release pellets

The development scientist has a great deal of flexibility when designing and creating oral dosage forms caused by pellets. Without modifying the formulation or the method, they can be separated into the appropriate dose strengths. They can also be combined to deliver particles with various release profiles or incompatible bioactive chemicals at the same or distinct locations in the gastrointestinal system.[6]

➢ **Advantages of extended release pellets**



Various Polymers used in Preparation of Extended release Pellets

❖ **Materials used**

- **Natural Polymer:** Hydroxypropyl methyl cellulose, Guar Gum.
- **Excipient:** Ethyl cellulose, polyvinyl alcohol, polyethylene glycol, methacrylic acid, Hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and Eudragit L.[19,20]

❖ **Drug release mechanisms**

The type and thickness of the coating, the type of drug, and the type of core all affect the mechanism governing drug release from reservoir-coated pellets, which is frequently a

complicated process. Diffusion across the continuous polymer layer encircling the drug-loaded center is one of the ways.[11] In order to get to the pellet core, water must first pass through the coating. The medication then dissolves and is released. The concentration gradient between the medication's interior and outside of the pellet (Ci) causes the drug to be released. Under ideal sink circumstances, the quantity of medication discharged (dM) during a certain period (dt) can be computed using Fick's equation of diffusion as follows.

$$Dm\backslash dt : Dm.A.K\ Ci\backslash d$$

K is the drug's partition coefficient (aqueous phase – polymeric phase), A is the surface available for diffusion, Dm is the drug's apparent diffusion coefficient in the polymeric film, and d is the film coating's thickness.[12] Regretfully, Fick's Law, which was originally designed to explain diffusion in binary mixtures, is not easily applicable to drug release from reservoir pellets. A homogenous, complete polymer sheet, for instance, is thought to have a constant diffusivity. It is known that many polymers swell when they come into contact with a medium, which eventually raises the diffusivity. Furthermore, crystalline areas seen in the majority of polymers are where drug dispersion is minimal.[13]

The so-called "jump-and-run" model has been used to describe drug dispersion in the amorphous areas of polymers. It was suggested that the homogenous, semi-crystalline structures of parallel-aligned polymer molecules are present in the amorphous regions of polymers. A "dead-end" (a crystalline region or a point of high chain entanglement) is reached when permeates, such as the diffusing drug, "run" along the tube between parallel polymer chains. There, the polymer chains are pushed and bent apart as they are compelled to "jump" from one tube to the next (Figure 5). Water-filled pores can release drugs.[14] These pores may result from substances that dissolve in water seeping 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.

$$\frac{dM}{dt} = Dp.A.\frac{\varepsilon}{\tau}.\frac{Ci}{d}$$

where ε is the volume percentage of the pores, τ is the tortuosity of the channels, and Dp is the drug's diffusion coefficient in the aqueous phase contained in the channels and pores.[15] Osmotic effects are another potential mechanism that regulates drug release from coated pellets. This method requires a semi-permeable membrane to enclose an osmotic active core and a differential pressure gradient between the membrane's inner and outer surfaces.

Drug and sugar core osmotic pressures, as well as the porosity of the polymeric membrane, determine osmotically driven release.[16] When the medication absorbs water, it is forced out through the coating's pores.

In this case, dV/dt represents water flow. θ represents the permeability of the polymeric membrane, l its thickness, A its surface area, and Δπ its difference in osmotic pressure (ignoring the opposing hydrostatic pressure). It is possible for one or more of the aforementioned mechanisms to control the overall drug release rate from coated pellets. Drug release rate is also influenced by parameters including core and coating swelling.[17] substance release rates can be significantly impacted by the type of substance. Multiple researchers have examined the way that drugs are released from ethyl cellulose films with pore formers. Osmotic pumping was responsible for medication release at lower pore former (HPMC) concentration, while diffusion also had a role in overall drug release in the presence of HPMC. Drug release from coated pellets was shown to be controlled by adding modest amounts of polyvinyl alcohol polyethylene glycol graft copolymer to ethylcellulose coatings, regardless of the drug's solubility or the kind of core formulation. Diffusion over intact polymeric membranes was demonstrated to be the mechanism governing drug release.

An additional element impacting the release of the medication mechanism is the polymer's glass transition temperature. The polymer was in a glassy form with water-soluble plasticizers after the plasticizer migrated and the medication permeated the water-filled pores. When the polymer was in the rubbery form with water-insoluble plasticizers, a two-phase release mechanism was discovered. Drug was liberated in the first phase via pores made by HPMC leaching, and in the second phase, pore shrinkage took place, resulting in a reduction of the polymer chains' free volume.[18] The type of coating process (aqueous versus organic) was discovered to have distinct effects on the mechanism of drug release. When ethylcellulose and an enteric polymer (ethylcellulose: methacrylic acid ethylacrylate copolymer, Eudragit L) were coated, the drug was released by diffusion through the intact polymeric films and/or water-filled gaps. Lower hydrostatic pressures were required to cause cracks to occur in aqueous coatings, though. Higher hydrostatic pressure was needed to cause fracture development in organic coatings because they were mechanically robust and had a high degree of polymer-polymer interpenetration.

- **MANUFACTURING METHODS**

➢ **Extrusion Spheronization Process**

Since the 1950s, when the idea of multiparticulate dosage forms was first proposed, there has been a growing interest in the techniques for creating multiparticulate prolonged release (CR) oral dosage forms. Spheronization and extrusion are two techniques that have become more popular in recent years. In the future, it is the preferred way for preparing multiparticulate CR dosage forms, and it has been widely considered as a promising technique. Dry mixing, extrusion, spheronization, wet granulation, drying, and screening are all steps in this multi-step process. The first procedure involves combining the medicine and excipients in an appropriate mixer and then wet granulating the mixture to turn the powder into a plastic.

Once the extruded strands come into touch with the rotating friction plate, they instantly break into short spherical rods and are propelled outward and up the processing chamber's stationary wall by centrifugal force. The cycles are repeated until the required sphericity is reached when the particles eventually fall back to the friction plate due to gravity. The multi-step process of extrusion-spheronization involves several equipment and unit operations. Nonetheless, the best part of the processing machinery determines the final pellet quality.[21]

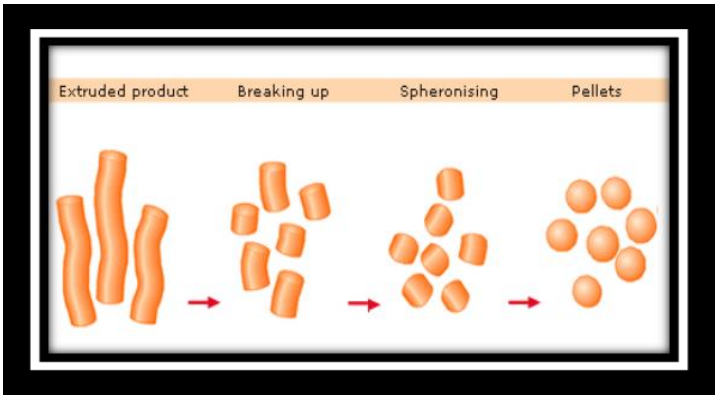


Figure 1: Extrusion Spheronization Technique.

➢ **Extrusion**

Extrusion is the process by which the moist bulk is shaped into long rods. Extruders can be divided into three categories: screw-fed, gravity-fed, and ram-fed. These extrusion machines differ in their design features and methods of operation. Screw-fed extruders can be either axial or radial, and they move materials horizontally by rotating their screws along a horizontal axis. Using jacketed barrels during extrusion increased the product's temperature. Screens positioned around the screws' horizontal axis allow the material to be extruded

radially in circular extruders, which have a brief travel zone. Rotating cylinder and revolving gear extruders are examples of gravity-fed extruders; their main distinction is the installation of two counter-spinning cylinders.

There are actually two counter rotating cylinders in the rotating cylinder extruder; one of them is hollow and perforated, while the other is solid and serves as a pressure roller. The piston in ram extruders pushes the materials through a die at the end of the process.[22] Ram extruders were chosen for formulation development since they were made to measure the formulation's rheological characteristics. To produce pellets with the necessary qualities in an extrusion-spheronization process, formulation elements including filler, lubricants, and pH modifiers are essential. The granular mass needs to be sufficiently cohesive, plastic, and self-lubricating in order to extrude. For the spheronization process to improve the formation of homogeneous spherical pellets, the extrudates must break at the proper length and have enough surface moisture. When extrusion spheronization is used, excipients are more crucial than in other pelletization processes. They provide strength and integrity to the pellets, aid in extrusion, and assess the spherecity of the wet pellets. In extrusion spheronization, microcrystalline cellulose (MCC) is the most often employed excipient, resulting in the creation of spherical spheres with desired properties.[23]

- **Spheronization**

In the third stage of the extrusion spheronization process, the extrudates are poured onto the friction plate, which is the spheronizer's rotating plate. There, they break up into smaller cylinders that are the same length as their diameter; frictional forces cause the plastic cylinders to round. Different phases of the spheronization process are identified based on the shape of the particles, ranging from a cylinder to a cylinder with rounded edges, dumbbells, and elliptical particles, finally culminating in perfect spheres. Another process for pellet formation may be present. After cylinders with rounded edges form in this mechanism, a cylinder twists and eventually breaks into two separate pieces.

Both sections have flat, spherical sides.[24] Certain pellets have a hollow formed by the flat side's edges folding together like a flower as a result of the rotational and frictional forces involved in the spheronization process. A normal product's spheronization takes two to ten minutes. For the friction plate to create a highly spherical pellet, it should rotate between 200 and 400 RPM. The majority of reports that show the usage of spheronization speeds more than 400 RPM stand in stark contrast to this notion. The explanation for this discrepancy is

that speed in conjunction with friction plate diameter matters more than speed alone. Those two factors are used to calculate the plate peripheral velocity, which should be compared to the friction plate's absolute rotational speed. To boost the frictional forces, the friction plate features a grooved surface. The grooves have two different geometries: radial geometry, which uses a radial pattern, and cross hatch geometry, which uses grooves at right angles.[25]

Figure 2: Spheronization Process.

- **Layering Process**

Solid inert cores are loaded with medications and/or excipients during layering procedures. Several techniques can be used to layer inert cores in an appropriate container like a fluid bed or coating pan. Spraying a solution or suspension that contains both the medicine and the binding agent onto the cores is one technique. Others involve directly layering the drug in powdered form, where adherence is guaranteed through the application of liquid bind to the core and drug loading happens by gravity.[26] Numerous little drug-loaded units that are placed into capsule for patient distribution can be produced using the layering technique.

When applied to circular inert core, like nonpareils, layering procedures from solution/suspensions result in uniform drug-loaded particles that maintain a roughly spherical shape. To increase the size of particle and provide the correct drug release profile, they are consequently especially well suited for successive film coating. Powder layering entails using a binding solvent to assist deposit successive layers of dry powdered medication, excipient, or both on performed nuclei or cores. It usually calls for specific equipment since powder stacking entails applying the wet and dry powders simultaneously. Equipment such as centrifugal fluid bed granulators and tangential spray transformed powder stacking processing as a pelletizing technique.

In case of tangential spray, the fluidization air and rotating disk give the necessary mixing. A centrifugal granulator with two walls is used for the process, which may be operated in both

open and closed modes. By closing the inner wall, powder layering allows liquid and powder to be applied simultaneously until the pellets reach the required size. After the inner wall is erected, the spheres go inside the drying area.[27] The air used for fluidization lifts the pellets back into the forming zone, passing over the inner wall. Up until the pellets reach the appropriate residual moisture level, the procedure is repeated. Figure 3 provides a comprehensive illustration of the several processes involved in the powder layering process.

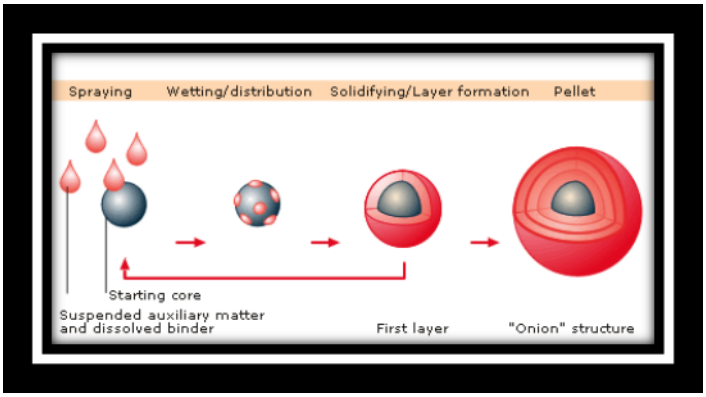
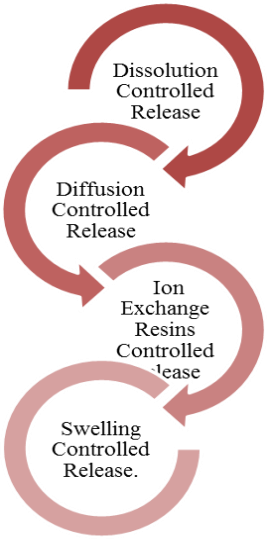


Figure 3: Drug Layering technique.

MECHANISM OF DRUG RELESE FROM PELLETS

The goal of creating an extended release dosage form is to create a dependable formulation that offers all the benefits of dosage form with immediate release without the possibility of dose dumping. The extended release material formulation has involved the employment of a variety of approaches. Generally speaking, prolonged formulations can be categorized according to the drug release mechanism.[28,29]



Dissolution Controlled Release

The two steps in this kind of controlled release are the drug molecules' separation from the solid structure's surface to the nearby liquid interface and their subsequent diffusion from the contact with liquid media in bulk.[30] This system's rate of dissolution and amount dissolved per unit of time may be computed using the Noyes-Whitney equation, which links the solid's and the dissolution medium's parameters to the rate of solid dissolution. The relationship is as follows.

dW \ dtL: DA (Cs – C)

Where,

dW/dt is dissolution rate;

A is the solidify area of surface;

C is the solid concentration in media of bulk liquid;

Cs is the solid concentration in the solid diffusion layer;

D is the coefficient of diffusion and

L is the thickness of diffusion layer.

Diffusion Controlled Release

The active component permeates the polymeric substance in this kind of controlled release device. These are primarily categorized as matrix and reservoir systems.[31]

Reservoir system

A lot of reservoir systems use cellulose derivatives. Its components are the coated membrane (the diffusion barrier) and the core (the reservoir). By way of the coated membrane, the active substance diffuses from the reservoir.[32] When membrane of polymer hydrogel encloses a drug depot in a system of reservoir, drug release via the membrane can be explained by Fick's first rule of diffusion.[33]

Matrix System

Matrix controlled release is given more weight in this review article when designing extended-release tablets.[34] Active and inactive chemicals are combined and uniformly distributed throughout the dosage form to form a matrix system. Many factors contribute to the success of matrix systems, which are by far the most widely utilized oral prolonged release technology. In matrix type formulations, the release follows ficks first law of diffusion.[35]

Ion Exchange Resins Controlled Release

Water-insoluble, cross-linked polymers with ionizable functional groups are known as ion exchange resins. In many pharmaceutical applications, the resins have been employed, mostly for controlled release systems and flavor masking. Ion exchange resins' capacity to swell has led to their application as disintegrants in tablet formulations.[36] As a result of the drug's extended exposure to the resin, it forms an irreversible compound with ionizable medicines. In the presence of ion-exchanged groups, the resin-bound drug is eliminated. The diffusion pathway's length and size, as well as the amount of cross-linked polymer in the resin moiety, control how quickly drugs are released.[37]

Swelling Controlled Release

The foundation of swelling-controlled systems is ER polymer swelling. Abnormal penetrate transport is observable as a result of the polymers' viscoelastic characteristics, which are strengthened by the cross-linked network.[37] Case II transport and pure Fickian diffusion both constrain this behavior. As a result, there are three main forces that drive transportation. The polymer network causes the osmotic force behavior, penetration concentration gradient, and polymer concentration gradient to be seen.[38] By preventing the implanted medication from releasing, an appropriate polymer can counteract typical Fickian diffusion, resulting in a longer duration of drug administration and perhaps zero-order release.[39]

Various formulation variables, including polymer grade and type, solubility of drug, ratio of drug to polymer, particle size of drug and polymer, pressure of compaction, and presence and absense of additives and excipients in the final formulation, in addition to the glassy-rubbery transition of the polymer (caused by water penetrating into the matrix, where the interaction between water, polymer, and drug or fillers is considered the primary factor for release control), can affect drug release from swellable matrix tablets.[40]

- **Freeze pelletization**

Making spherical pellets for use in pharmaceuticals is made easy and novel by the process of freeze pelletization. This method involves introducing a molten-solid carrier or matrix as a droplet into column of inert liquid medium where the molten solid is not soluble.[41] As droplets, the molten solid travels through the liquid column before solidifying into spherical pellets. The molten-solid droplets may contain sorbitol, maltose, Geluciers having higher increased hydrophilic-lipophilic balance value (HLB:14), water-soluble polyoxyethylene derivatives (like Brijs), copolymer pf polypropylene and polyethylene, poly (ethyleneoxide)

(PEO) derivatives, PEG derivatives, PEG–PEO derivatives, or different combinations of these.[42]

Silicone oils, mineral oils, vegetable oils, aliphatic long-chain hydrocarbons, and other mixtures are totally incompatible with these substances when melted. For the liquid in the column, commercial silicone oils with a broad variety of viscosities work best[43] Mostly inert, they are transparent, harmless, and nonrancidifying. Furthermore, their freezing points are extremely low. Pellets made from molten, hydrophilic solids would be suitable for use with Apparatus I since their densities are typically higher than those of these liquids.[44]

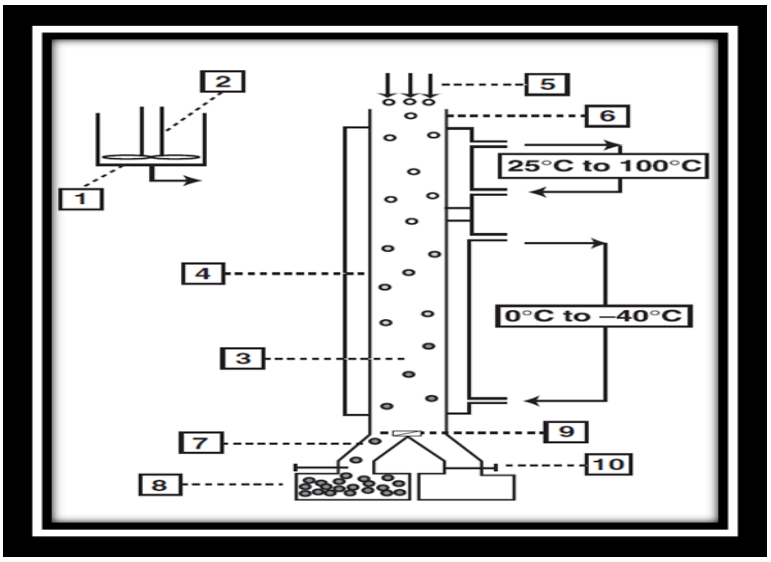


Figure 4: Schematic of Apparatus I.

- **Hot Melt Extrusion**

To address the issues with pellets made using layering and extrusion spheronization techniques, the pharmaceutical industry uses melt agglomeration and hot melt extrusion techniques.[45], The instability issue caused by the presence of water during processing and storage is resolved by this procedure. The drug release from pellets made using these methods is also diffusion regulated, thus no extra film coating is needed.[46] There is a little distinction between these two approaches. In the process of melt agglomeration, solid tiny particles are agitated, kneaded, and layered in the presence of a molten binding liquid to form agglomerates.[47]

As a binding liquid that is molten cools and hardens, dry agglomerates are produced. The procedure for melt pelletization and melt granulation are common instances of melt agglomeration. The agglomerates' size and shape would gradually alter throughout the

agglomeration process.[48] Granulation and pelletization are often difficult to differentiate from one another. When extremely spherical agglomerates with a restricted size distribution are formed, granulation is therefore regarded as a pelletization process. Granulation, on the other hand, might be used to describe a failed pelletization process.[49]

DRUG PROPERTIES OF EXTEBDED RELEASE FORMULATIONS

The scientist creating the extended release delivery system is especially interested in the limitation enforced by the drug's characteristics. Additional elements that are considered at every stage of design process include the patient, the condition that is being treated, the length of therapy, the route of medication delivery, the type of delivery system, and the drug's properties. The following categories apply to these properties.

(a) Physicochemical

(b) Biological properties

These characteristics most significantly impact how the medicine behaves in the body and in the delivery mechanism. Since the biological characteristics of a medicine are determined by its physicochemical characteristics, there is no precise differentiation between these two groups. In vitro experiments are by definition the source of physicochemical properties, while pharmacological studies and standard pharmacokinetic studies of a drug's distribution, absorption, metabolism, and elimination (ADME) characteristics yield biological properties.[50]

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

COATING TECHNOLOGY FOR CONTROLLED RESELES PELLETS

❖ **Functional coating materials (enteric coatings, sustained-release coatings)**

Enteric coating

Usually composed of natural or synthetic polymers, the enteric coating is an outer layer that can be applied to oral medicinal dosage forms. Enteric coating may be used to change the taste or smell of the medication, protect against environmental factors (particularly pH), shield the stomach mucosa from the irritating effects of certain medications, or enable site- or time-specific drug release, among other reasons. A medicine can be released in the small intestine but cannot be delivered in the stomach due to the enteric coating.[51]

To accomplish this, a polymer that is permeable at intestinal pH but not soluble at pH of acid is employed. The coating melts to release the medication once it enters the upper portion of small intestine. Methacrylic acid copolymers, cellulose acetate phthalate, and hydroxypropyl methylcellulose are phthalate are among the polymers frequently utilized to create enteric coatings. These kinds of covers can be made using technological processes like sugar coating and film coating.[52]

Kinds of polymers for enteric coating

Enteric coatings often use polymers with carboxylic acid in their framework; the quantity of carboxylic groups in these polymers determines how soluble they are. The chemical makeup of enteric coating polymers can be used to classify them.

- **Polymethacrylates**

Free radical addition polymerization is used to create these artificial polymers, which contain different kinds of methacrylates in certain ratios. Sold under the brand name Eudragit®, they have numerous uses for drug delivery, including colon drug delivery and enteric coating.[53]

- **Cellulose derivatives**

Potential uses for intestinal coatings of pharmaceutical formulations include cellulose esters like cellulose acetate succinate (CAS), cellulose acetate trimellitate (CAT) and cellulose acetate phthalate (CAP). Acetate succinate (HPMCAS) or hydroxypropyl methylcellulose phthalate (HPMCP)-containing cellulose ether esters can also be utilized for enteric coating.[54]

- **Polyvinyl derivatives**

The enteric coating polymer polyvinyl acetate phthalate (PVAP) raises the resistance of tablets and capsules to changes in the stomach's acidic pH and exhibits pH-dependent solubility.[55]

- **Other materials**

Additional substances that could be utilized for enteric coating include dextrins, zein, amylose starch, shellac (aleuritic acid esters), and starch derivatives.[56,58]

Shellac Coating

A crucial coating ingredient for food items is shellac. Since the advent of aqueous ammoniacal solutions, its significance for pharmaceutical applications has also returned. Shellac's rather high pH of dissolution means that additional additives are needed if it will be utilised as a substance for enteric coating. Shellac's dissolving behavior, however, might be useful for situations involving colon targeting or continuous release. Theophylline pellets with instant release were coated with shellac after being coated with various subcoats that contained citric acid, calcium chloride or Eudragit® E, respectively. The resulting pellet compositions' drug release was measured. We used FT-IR spectroscopy to study the internal workings of interactions between the shellac coating and the modifying subcoat components.[59]

Drug release was extended in all compositions with modulating subcoats. Citric acid had the impact of reducing the amount of dissociation of shellac, whereas calcium chloride had the effect of ionic associations with shellac. The solubility properties of this fundamental polymer provide an explanation for Eudragit® E's influence. A simple and efficient way to obtain prolonged absorption from shellac-coated medication is to apply modifying subcoats. Customized sustained release profiles are possible through the selection of an appropriate material and the modification of its concentration.[60]

Multi-layered pellet systems

Pharmaceutical preparations of this type are becoming more and more common on the market, and multiparticulate dosage forms of this type have become very popular in recent years. In comparison to single-unit systems, microparticulates are flexible drug delivery methods that provide a great deal of design and development freedom for pharmaceutical dosage forms.[61] Without any more formulation difficulties, weighing the required number of

pellets makes it simple to manufacture various dosage units. The formulation of microparticulates into immediate-release or modified-release dosage forms is simple.[62] By using specialized film-coating techniques, a medication can be delivered to a particular site of action in the gastrointestinal tract (GIT).[63,64] Because these multiparticulate systems are less reliant on stomach emptying, the gastrointestinal transit duration varies less.

They are also more widely dispersed and less likely to irritate the same area of the GIT as larger medication concentrations. Furthermore, the creation of controlled-release formulations commonly involves the use of pellets. A regulated release with a reduced danger of dose-dumping is particularly possible with MUPSs, according to recent study.[65] Pellets made from two or more chemically incompatible medicinal ingredients can be given in a single dose unit.[66] Multiparticulates allow for the creation of sprinkle capsules, which is very helpful for elderly or juvenile patients who have trouble swallowing. The contents of these capsules can be suspended in a beverage or mixed with a small quantity of semisolid food to make absorption easier.[67,69]

Drug layering or direct pelletization are the two methods used to create multiple-unit pellet systems. Drug-containing pellets are made with a drug integrated into their cores; drug-layered pellets are made with beginning pellets coated with a drug that creates an outer layer on the exterior of inert cores. Erosion and spheronization of a powder blend containing a drug ingredient and at least one excipient are typically used to accomplish direct pelletization. In drug layering, the drug particles are deposited on the outer surfaces of starting pellets (inert cores), typically with the aid of a binder, which is a polymer that is approved for use in pharmaceuticals.[70, 71]

Compared to single-unit systems (conventional tablets or capsules), drug stacking atop inert starting pellets results in greater surface area, improved drug dispersion, enhanced breakdown, and ultimately improved bioavailability. Various polymers can be applied to these drug-loaded pellets to change their dissolving properties, protect them from external factors (e.g., moisture protective coating), or shield them from the stomach's acidic conditions (enteric coating).[72,73]

CHALLENGES AND FUTURE PERSPECTIVES

Stability and scalability concerns

The curing stage is necessary to finish the film production process, but it has been observed that the drug release rate decreases, particularly under high humidity conditions. More slow polymer coalescence, which produced denser films and reduced permeability for drugs and water, was primarily responsible for this. Polymers having a substantial glass transition temperature were also shown to alter medication release characteristics. Brittle films and micro-ruptures in the film coat throughout storage can both result in faster drug release. Thermal humidity curing has been shown to improve polymeric film coalescence; however, excessive humidity during storage might destabilize films, leading to gradual alterations to the drug release rate.[74]

Innovations in pellet formulation (nanotechnology, bio responsive polymers)

Table 5: Marketed products of extended release tablet.

Brand name	Strength	Company
Volix	Voglibose 0.3 mg	Ranbaxy
Seroquel XR	Quetiapine fumarate 150 mg	Astrazeneca
Ovarine – F	Clomiphene citrate 50 mg	Matrix pharma
Lostaz	Cilostazol 50 mg	Matrix pharma
Urocit –K	Potassium citrate 1 gm	Orphan Australia

Table 4: Examples of drugs marketed as pellets.

No.	Drug	Manufacturer	Product	Therapeutic class
1	Omeprazole magnesium	Astra Zeneca	Losec MUPS	Antiulcer
2	Esomeprazole magnesium	Astra Zeneca	Esomeprazole	Antiulcer
3	Metoprolol tartrate	Astra Zeneca	Toprol XL	Antihypertensive
4	Lansoprazole	Takeda	Prevacid solu Tab	Antiulcer
5	Theophylline	Key	Theodur	Antiasthmatic

EVALUATION OF PELLETS

- **Pellets size**

Pellet size determination is crucial since it influences the pellets' flow characteristics. The kinetics of drug release from the pellets are also influenced by particle size. There are several methods for determining particle size. The straightforward and uncomplicated procedure

involves choosing an appropriate mesh size and shaking it with a mechanical shaker. Size determination can also be done with a vernier calliper.[75]

- **Flow properties**

Different methods, such as the Hausner's ratio, Carr's index, and angle of repose, can be used to measure flow parameters. The uniform size distribution can be inferred from the flow properties.[76] Surface characteristics utilizing scanning electron microscopy, the formed pellets' surface characteristics and cross section may be examined. For assessing the smoothness of the pellets' surface, further methods include optical microscopy and the use of a non-contracting infrared profile meter.[76]

- **Surface morphology**

Pellets' cross section and surface morphology are analyzed utilizing scanning electron microscopy.[77] Mounted on the aluminum stub, the collected pellets are flare-coated with just a small amount of platinum using a sputter coating apparatus (Polaron, UK) in an argon environment prior to being examined using a scanning electron microscopy. Initially, Sood et al. (2004) reported using optical microscopy to analyze the microstructure of the pellet surface.[78] Eurrkainea and Lindqvist (1991) conducted a study using SEM images to examine the effects of various fillers and found that MCC and maize starch produce the highest-quality pellets with a smooth surface. Utilizing a non-contracting laser profilometer, the study of pellet surface roughness was investigated.[79, 80, 81]

- **Specific surface area**

Pellets' size, shape, and surface area are all directly correlated. Surface area information is desirable, particularly when film coating is taken into account. When it comes to uncoated pellets, it is crucial to understand the surface area because it affects drug release. The process of gas adsorption is used to calculate the particular surface space of pellets.[82]

- **Mathematical calculations**

A spherical pellet can be identified by its diameter and is smooth and compact, with the least amount of surface space per unit volume. Given that the total area is approximately $\pi r2$, The particular amount of surface can also be ascertained using measures of true density.

- **Hardness and Friability**

Pellets' mechanical qualities are crucial for processing. When pellets break of during handle of, transportation, storage coating, plus additional unit function, dust is produced. Variations in the raw ingredients, pellets composition and manufacturing method can result in significant differences in their hardness and/or friability.[83] Although it may not be precise, the Kahl pellet-hardness tester is able to quantify the hardness of pellets. To assess the friability of pellets, glass beads of a specific diameter are combined with an Erkewa type a turbula mixture or tablet friabillator for a predetermined amount of time. This creates abrasion and a friability index. Another method for determining friability is to use a fluidized bed with a Wurster insert and a stream of air.[84]

Mechanical tests

- **Tensile Strength**

Using a 5 kg load cell and tensile equipment, the pellets' tensile strength is assessed by straining them until they break. The failure load value and the pellets' radius are used to compute the tensile strength once the load has been recorded.[85]

- **Cushing strength**

Utilizing a Material Testing Machine, the elastic modulus and crushing strength (the load required to shatter the pellets) of 15 pellets (850–1000 mm size fraction) were ascertained. A 1 mm/min speed was chosen for the uppermost mobile platen equipped with a 1 kN load cell. The device was equipped with a computer system that produced force-displacement and elastic modulus graphs.[86]

- **Density**

Bulk and tapped pellet density is simply determined by USP density instrument and can be influenced by changes in formulation or process that may affect other processes or aspects like filling and packaging characteristics during shell manufacture and tablet compression. An automated tapper can measure the bulk density of pellets, and an air-comparison pycnometer or solvent displacement method can determine the actual density of pellets. The packing characteristics of pellets or spherical seeds, which deliver larger bulk densities because of tiny intraparticle porosities, are shown by bulk density.[87,88] The degree of pellet densification or compactness is indicated by the true density.

- **Pellet surface roughness**

Measurements of surface roughness were performed on the same pellet samples that were used to determine the diameter. After mounting the samples on a black, non-reflective plate and setting it on an air-bearing table, a laser profilometer was used to evaluate the surface roughness. The sensor had an aperture angle of 53 degrees and a light spot diameter of 1 mm. Measurements were made in three dimensions with a depth of ±50 m and a frequency of 100 points. With a resolution of 1000 points/mm, the area scan was performed across the 2.00mm x-transverse and the 0.20mm y-transverse, having a resolution of 200 points/mm.[89,90] Qr (establish mean squared error of the asperity the height distribution), Rtm (average peak-to-valley ratio), and Ra (rugosity) were the roughness descriptors assessed. The results are the arithmetic mean and standard deviation of five replicates of the above procedure.

- **Porosity**

Medication release from the pellets is influenced by the porosity of the pellets, which alters the capillary action of the dissolved medication. Using mercury porosimetry, the porosity of the pellets can be quantitatively determined. Using SEM and image analysis, the pellets' porosity can also be assessed subjectively.

- **Surface area**

When pellet coating is necessary, surface area is regarded as a crucial characteristic. The pellets' size, shape, and surface area are directly correlated. To find the specific surface area, the gas adsorption approach is employed.[91]

- **Friability**

The purpose of the friability test is to assess the pellets' tensile and mechanical strength. To assess friability, a tablet friabilator is utilized. For determining friability, a fluidized bed with a Wurster insert and an air stream can be utilized.[92]

- **Pellets shape**

One of the pellets' other crucial characteristics is their shape. The pellets ought to be round. There are various ways to determine the form of the pellets. You can utilize both stereomicroscopy and microscopy. An indirect technique for determining the cylindrical form of the pellets is the angle of repose.[93]

- **Disintegration time**

One of quick release pellets' primary features is their disintegration. A tablet disintegration test was conducted by Thommes and Kleinbudde in a specially designed tablet disintegration tester by inserting special transparent tubes of a specific diameter and length with a sieve of 710mm mesh size during the top and bottom of the tube.[94] Huyghebaert et al. (2005) reported disintegration tests employing the rotating cylinder method (USP Apparatus 3).

- **In-vitro dissolution studies**

The last forty years have seen a widespread recognition of the importance of studies of in-vitro dissolution in both medication development and quality evaluation. For the modified-release pellets, these studies were conducted to determine a correlation between experimental release and in vivo absorption, as well as to examine the release behavior of various formulations in various dissolution medium. A quality control parameter is established by combining the in vivo/in vitro correlation with the release of the drug from the solid dosage form, which frequently serves as a determining stage in the in vivo absorption process. Using USP Apparatus I or II82, the composition, hardness, and size of the pellets are the primary determinants of the drug's release from them.

The drug's water solubility, physical condition within the pellet, the polymer and binder utilized, the presence of additives like surfactants, and other factors all affect the medication's release profiles from pellets. When wax-based freeze-dried pellets were used, the drug release rose with increasing water drug solubility and decreased with increasing wax hydrophobicity.

APPLICATIONS OF EXTENDED RELEASE PELLETS IN TARGETED DRUG DELIVERY

Pellets have varied applications in a number of industries and an innovative use of it’s could achieve maximum profitability.

Taste masking

Pellets are useful for items that need to have a flawless taste abatement. While many methods have been used to cover up a drug's bitter taste, including adding flavors and sweeteners, filling capsules, coating with water-insoluble or pH-dependent insoluble polymers, complexities with ion-exchange resins, micro-encapsulating with different polymers, complexing with cyclodextrins, and chemical modifications like using insoluble prodrugs, very few reports have discussed how to cover up an unpleasant taste without reducing

bioavailability, particularly for oral products. Because of their large surface area, the pelletization process addresses the challenging flavor masking issue while preserving a high level of bioavailability, particularly for oral products.

Additionally, pellets do not contain dust fractions, which are uncoated bits that could cause taste issues, due to the unique design of the production process. Antibiotics (roxithromycin, cephelexin, and clarithromycin) and bitter-tasting anti-inflammatory medications are among the many items that can now be made to have excellent patient compliance, potentially enhancing the product's sales in pharmaceutical marketplaces.[95, 96]

1. Immediate release

Drugs administered in pellet form have area of surface larger than conventional compressed tablets and capsules, which might be used to create fast dispersible tablets and significantly shorten the disintegration period.[97]

2. Sustained release

Due to the beads' continuous progression from the alimentary canal into the small intestine, the pellet form offers a gentler absorbing characteristic from the gastrointestinal tract. The production of pharmaceuticals in dosage form which is sustained release is increasingly utilizing pellets. It is commonly recognized that the dose form has advantages.[98, 99]

3. Chemically Incompatible Products

Sometimes delivering such chemicals in only one dose is necessary. Pellets can be given in a single capsule, however in the compacted tablet dosage form, individual tablets would need to be given.[100]

4. Varying dosage without reformulation

Because of their superior flow characteristics, pellets are suitable for filling capsules and allow the manufacturer to change the dosage by altering the size of the capsule without having to reformulate the product.[101,102]

CONCLUSION

Nowadays, many medications are sold in a range of extended-release forms. Only those, nevertheless,that lead to a notable decrease in the frequency of doses or in dose-related toxicity are likely to enhance therapeutic results. Treatment response will be influenced by meal presence, gastrointestinal motility, and concurrently delivered or present material. The

marketplace for extended release medication administration has advanced significantly and is expected to keep expanding. We came to the conclusion that pellets are used in pharmaceuticals and are made mostly for oral extended-release dosage forms with gastro-resistant or extended-release, extended-release, or site-specific drug delivery capabilities. Gelatin capsules that are hard or tablets are used to give coated pellets for these purposes.

Extended release pellets are becoming more and more important in the creation and manufacture of dosage forms as drug delivery methods get more advanced. There is flexibility in target-release features when medications are formulated in multiple-unit forms of administration, such as compressed tablets or extended-release coated pellets packed in capsules. When compared to alternative dose forms, the formulation is more safe and effective.

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