REVIEW ARTICLE

A Review: Miracle of Pelletization Technique in Drug Delivery and their Future Perspectives

Vishal Gupta, Jitendra Gupta*

Department of Pharmaceutics, Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India

Abstract

Pelletization is the process of agglomerating tiny powders or particles of a bulk active pharmaceutical agent and raw materials to create small, free-flowing pellets that are roughly spherical in shape. The future trend of pellet dosage forms involves enhanced drug delivery, controlled release, and improved patient compliance. Innovations include personalized medicine, targeted drug delivery, and multifunctional pellets for complex therapies. One key of pellet dosage forms is their ability to enable controlled and sustained drug release, enhancing therapeutic efficacy and reducing side effects. Ultimately, technology contributes to improved patient outcomes and quality of life. However, the future holds even more promise, as integrating nanotechnology and biodegradable polymers is anticipated to revolutionize the design of pellets, enabling precise control over drug release kinetics and enhancing therapeutic efficacy.

Key words: Pellets, pellets dosage forms, pellets technologies

INTRODUCTION

The continuous rise in the global population facing the menace of the deadly disease cancer calls for effective remedial measures with the most minor side effects. Cancer could be one of the most dangerous global health issues. As of now, it ranks as one of the top global causes of mortality, with 2,001,140 new cases and around 611,720 cancer-related deaths reported in 2024. Forecasts suggest that the number of new cases could rise by nearly 70% over the next two decades.[1]

The abnormal growth of cells causes cancer and is challenging to treat because cancer cells are not recognized as foreign by the immune system. Standard treatments involve surgery, radiation, and chemotherapy, depending on the cancer type and stage. On the other hand, these practices have a detrimental effect on overall bodily health. Furthermore, metastasis is frequently incurable, mainly when local treatments, such as radiation and surgery are used. Therefore, the primary task is to discover a drug delivery system that effectively eradicates cancer cells while sparing healthy cells.[2]

Cancer is a disease that originates from uncontrolled cell proliferation that invades, erodes, and destroys healthy cells while also spreading to nearby tissues. Genetic modifications are another term for most DNA alterations in genes that cause cancer.

Tumors exist in the following types (a) Malignant tumors spread to other areas in the body. (b) Benign tumors (non-malignant) stay in one place. Malignancy, another name for cancer, is the aberrant proliferation of cells. More than a hundred different forms of cancer exist, such as lymphoma, skin, lung, colon, prostate, and breast cancer. Symptoms vary based on the type.

Cancer that originates in the lungs is most frequently found in smokers. A family history of the disease, as well as exposure to certain chemicals, smoking, and secondhand smoke, are among the causes of lung cancer. Chest pain, wheezing, cough in blood, and weight loss are among the symptoms. Often, until the cancer has progressed, these symptoms are not apparent themselves.

Address for correspondence:
Jitendra Gupta, Institute of Pharmaceutical Research, GLA University, Mathura - 281 406, Uttar Pradesh, India.
Email: smartjitu79@mail.com

Received: 20-01-2025
Revised: 08-03-2025
Accepted: 18-03-2025

TYPES OF BLOOD CANCERS

Cancers are classified as indicated in Table 1.

SIGNS AND SYMPTOMS OF CANCERS

a. Persistent cough with blood or trouble breathing
b. Significant weight loss and fatigue
c. Blood in urine
d. Changes in bowel or bladder habits
e. A lump anywhere on your body
f. Skin alterations, including skin blisters and yellowing, darkening, or reddening.

Leukemia is a type of cancer that starts in the bone marrow's blood cells, specifically from hematopoietic stem cells (lymphoid or myeloid). It leads to the uncontrolled proliferation of abnormal cells called blasts, which can spill into the bloodstream and infiltrate other tissues, such as the spleen and lymph nodes. Acute leukemias are characterized by rapid symptom progression and can cause bleeding problems when blast counts exceed 50,000/mm^3.

Lymphocytic leukemias involve immature lymphocyte progenitors that spread from the bone marrow to other tissues, while myelogenous leukemias disrupt the production of key blood cells. Both acute lymphoblastic leukemia and acute myelogenous leukemia (AML) present similarly and constitute nearly half of all new leukemia cases. The incidence of AML increases with age, making it more common in adults, while it is also the most frequently diagnosed cancer in children, especially between ages 2 and 9.

Though the exact causes remain unclear, risk factors include genetic pre-disposition, disorders, such as Down syndrome and Fanconi anemia, and the human T-cell leukemia virus. Complications can include disseminated intravascular coagulation, infections, and leukostasis, leading to severe outcomes, such Fanconi as bleeding or kidney failure.

Table 1: Types of blood cancers

Types	Description
Carcinomas	This type of cancer usually originates from cells in the endodermic or ectodermic germ layer during embryogenesis. It starts in a tissue found on both the inner and outer borders of the body
Myeloma	This particular type of cancer develops from mesenchymal origin or transplanted cells
Lymphoma	It is a blood cancer that occurs when T and B cells transform and start expanding and proliferating uncontrolled
Leukemia	Blasts, or the overgrowth of immature white blood cells, are a defining feature of bone marrow cancer.

Lymphoma is a type of blood cancer characterized by the abnormal proliferation of lymphocytes, a type of white blood cell. It often affects areas, such as the spleen, bone marrow, and lymph nodes, resulting in solid tumors. The causes are mostly unknown, and common symptoms include fever, chills, fatigue, and swollen lymph nodes. Treatment typically involves radiation therapy, chemotherapy, or bone marrow transplantation. While lymphocytes help the immune system fight diseases, their abnormal behavior in lymphoma can disrupt normal cell formation. Some types of lymphoma can be fully cured if treated promptly.

In multiple myeloma, plasma cells in the bone marrow produce antibodies to support the immune system. However, these cells can become cancerous, leading to the development of tumors outside the solid bone. This process gradually deteriorates bones and hinders healthy blood cell production. The specific cause of multiple myeloma is unknown. In the bone marrow, B lymphocytes, or plasma cells, create antibodies, which are crucial for immune defense. When myeloma develops, these cells behave abnormally, proliferating and forming tumors that compromise bone function.

Several promising cancer treatment approaches, including immunotherapy, photodynamic therapy, hypothermia, targeted therapy, and angiogenesis inhibition, are being researched. A cutting-edge strategy involves using multiunit particulate systems that conceal and protect medications until they reach cancer or tumor cells.[3,4]

PELLETIZATION

Pelletization is the process of agglomerating tiny powders or particles of a bulk active pharmaceutical agent and raw materials to create small, free-flowing pellets that are roughly spherical in shape. Pellets are collections of finely ground excipients as well as bulk drug granules. Small, freely flowing spherical or hemispherical solid units, typically ranging in size from 0.5 to 2 mm, constitute these entities. The standard method of administration for these is oral. Based on the intended use, these spheres have different diameters. Applications can be found in agribusiness (such as fertilizer), the polymers industry, and the pharmaceutical industry [Table 2].[5]

Pellets, which are small, round particles, are generally used in the pharmaceutical industry. They are formed by combining powders or granules containing active ingredients and raw materials using specialized equipment. Conventionally, the term "pellet" has referred to a broad range of geometrically shaped agglomerates, created from diverse raw materials and processed under different conditions.

In the early phase of the 1950s, it came to the pharmaceutical industry to get a response to a sustained release or extended release of drugs in formulations. Various methods produce pellets, such as stacking drug solutions, extrusion,

spheronization, and agglomeration from roto-granulators, suspending or spraying powder on inactive cores, compressing, spray drying, and spray congealing. The most recent advancements in the pellet are:-

a. They aid in the development of various dosage forms with modified release profiles, including immediate and extended-release options
b. They help mask the unpleasant taste of bitter medications
c. They come in mouth-melt pellet form
d. Polymer-based pellets to regulate the release of drugs schedule
e. As quickly dissolving tablets that include micro-pellets
f. The self-emulsifying pellets' function.
g. Floating pellets with Gastro retentive properties, etc.

PELLET CREATION AND GROWTH

The following steps are recommended as part of the pellet generation and formation mechanism.

Nucleation

In pelletization or granulation, nucleation happens when a powder is moistened, forming liquid bridges between particles and creating air-liquid nuclei. As bonding strength increases, particle size decreases. The rate and size of nucleus formation are influenced by factors such as original particle size, moisture content, viscosity, wettability, and processing conditions, such as tumbling and drying rates. After nucleation, growth mechanisms, such as layering and coalescence affect later phases.

Coalescence

Coalescence is when well-formed nuclei randomly collide to create big particles. It depends on a small amount of extra moisture on the nuclear surface. During this stage, the system's total mass stays constant, but the number of nuclei decreases. Layering is a gradual growing process in which a nucleus has already been produced, and further pieces and particles are added one after the other.

Layering

The number of particles in the layering stage stays constant, but as a function of time, the particle sizes get bigger, increasing the system's overall mass. Particle size decreases brought on by breakage, shatters, and attrition might end up in fragments or tiny particles. Large pellets collect the particles and pieces generated during size reduction. The formation of particles slows down the growth rate of pellets, followed by layering and coalescence until the number of beneficial coalitions declines significantly.

Abrasion transfer

"Abrasion transfer, the bidirectional movement of raw material between granules, is the key factor affecting the tiny growth of agglomeration during the ball formation stage. The mass or total number of particles remains unchanged in this scenario. However, as long as the circumstances that result in the material transfer are there, the particles experience a constant change in size."

LIST OF PELLETIZATION TECHNIQUES OR PROCESSES[16]

Extrusion-spheronization technique[32]

Extrusion spheronization is a standard multistep procedure used to produce pellets with a high loading content of active ingredients, uniform size, and good flow properties.

The principles for the extrusion spheronization technique are as follows-

Dry mixing

To achieve a uniform powder dispersion, the ingredients are dry-mixed using equipment such as a tumbler mixer, planetary mixer, twin shell blender, or rapid-speed mixer.

Wet massing

Common equipment and methods utilized in wet granulation are used to create an adequate plastic mass for extrusion. The brief technique process is as follows:

Extrusion

In this process, wet mass is pressurized and passes through an optimized or validated opening of the die plate screen to produce rod- or cylindrical-shaped particles of uniform diameter with enough plasticity and mechanical strength. Shaping wet mass into long cylindrical rods is commonly referred to as "extrusion."

Spheronization

"Commonly referred to as the "Merumerizer," this process focuses on creating spherical, uniformly-sized pellet particles. It contains a stationary cylinder and a rotating friction plate. Plastic materials are extruded and cut into tiny cylinders, each having a length that matches their diameter. Frictional forces cause cylinders to become rounded. This process is typically depicted using two geometric type patterns: A cross-hatched pattern with grooves intersecting at right angles and a radial pattern extending radially from the center of the disc [Figure 1].

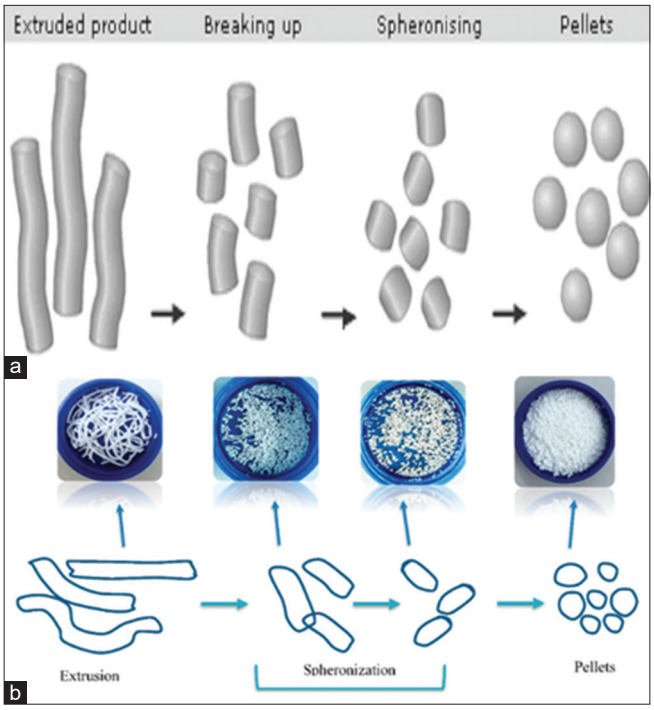

Figure 1: (a and b) Extrusion and spheronization process to produce pellets

SOLVENT-FREE COLD EXTRUSION SPHERONIZATION

"In 2003, Breitkreutz *et al*. introduced this method to effectively create taste-masked formulations for pediatric use. Unlike hot-melt processes, solvent-free cold extrusion does not involve high temperatures. The process includes binding the active pharmaceutical ingredient with a lipid-based binder that contains a glycerol-based hard fat, followed by cold extrusion of the mixture and spheronization of the extrudate to produce pellets. During the spheronization phase, these pellets develop a taste-masked lipid layer on above the upper surface."

EXTRUSION-SPHERONIZATION THROUGH MELT TECHNOLOGY

The procedure involves pumping raw materials using a rotating screw at a high temperature, which is then pushed through a die to create a product with a consistent shape. The rotating screw helps to mix and agitate the materials, breaking down any clumps and creating a more even distribution throughout the molten polymer.

Drug-layering technology

Drug layering, a key step in pharmaceutical manufacturing, is the process of adding layers of active pharmaceutical ingredient molecules onto nuclei, which can be granules, crystals of the same material, or non-Pareil seed. This is done using a solution, dry powder, or suspension. In the solution or suspension layering method, drug particles are dissolved or suspended in a binding liquid. In the powder medicine layering method, the powder is applied on top of inert seeds that have already been prepared and coated with a binder solution.

Powder-solvent layering technique

In powder-layering, low liquid saturation prevents complete drug dissolution. The process begins by spraying a binder onto nuclei and adding powder. In a rotating pan, nuclei collect powder, forming layers that adhere through capillary forces. Additional liquid and powder are added until the desired pellet size is reached. Upon drying, the binder crystallizes, forming solid bridges. Spraying with a binder may also lead to moisture absorption by fines, initiating nucleation [Figure 2].

Suspension/solution layering technique

Coating a core with a suspension or solution is ideal for pellet formation. Spraying the layering fluid allows for the application of the active substance at the desired concentration. Film coating typically follows this process. The quality of the initial active pellet is influenced by the coated pellets, which should be round, smooth, and have a narrow particle size distribution. The goal is uniformly rounded pellets with a dense structure and even surface, optimized for various product characteristics based on the active substance used [Figure 3].[19]

Dry-powder layering technique

Dry powder layering is the most effective method for pellet formation in the pharmaceutical industry. It involves coating a starter core with powdered ingredients using a binding solution, which reduces processing time and improves efficiency compared to liquid layering. With optimal conditions, weight gains of up to 300%/h can be achieved. The rotor process introduces micro-fine substances through a powder nozzle, resulting in dust-free, spherical pellets with a significant particle size distribution.

The powder is blended with a coating solvent and subjected to centrifugal motion, causing acceleration and impact that create agglomerates, which are rounded into dense pellets. The rotation speed affects the pellets' size and density. Finally, the wet pellets are dried in a fluid bed dryer.[22]

Spray granulation technique

The Wurster process is a highly efficient method for the controlled release of active ingredients, significantly reducing the need for excess coating materials. A strategically

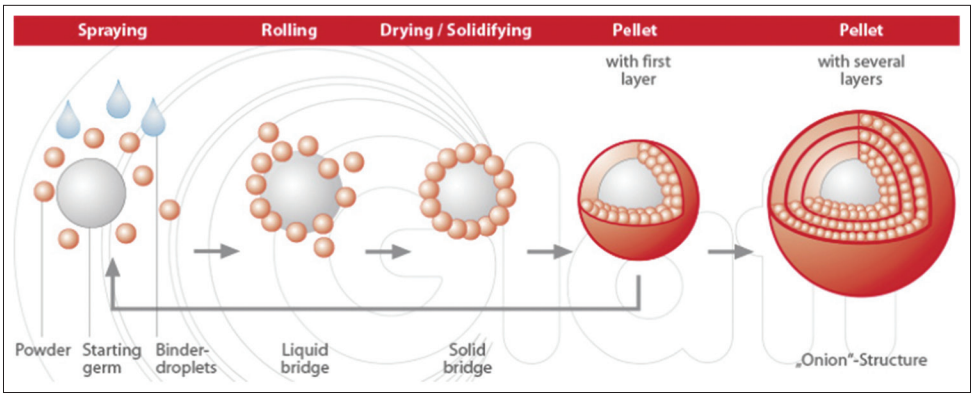

Figure 2: Powder solvent layering process to produce pellets

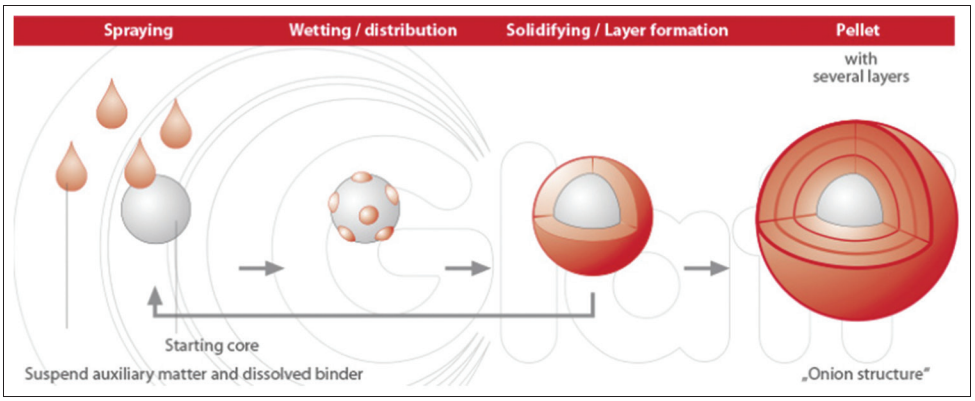

Figure 3: Diagrammatic representation of suspension/solution layering technique

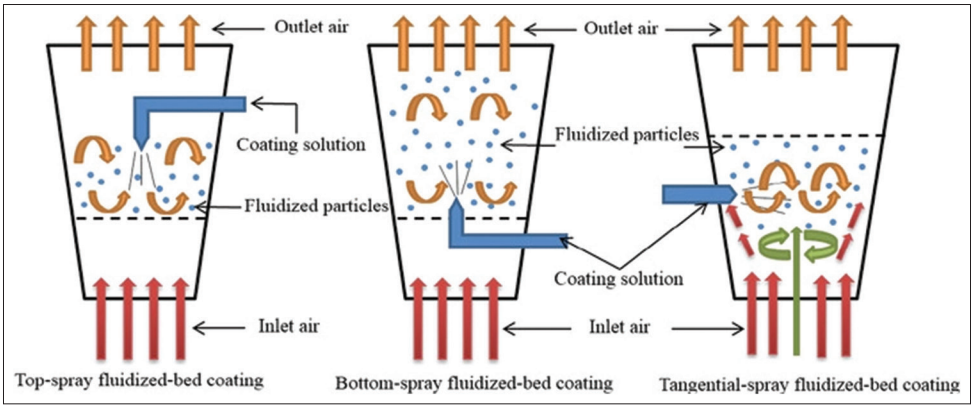

Figure 4: Diagrammatic representation of spray granulation technique (top spray, bottom spray and tangential spray granulation)

positioned spray nozzle within the base plate generates an optimal droplet pattern that enhances particle coating in the Wurster tube.

Particles are introduced into the spray cone, where they dry and return to the base plate, creating an effective coating cycle. They are then re-injected for accelerated spray action, ensuring uniform coating across all sizes. This fluidized bed spray granulation produces round, dust-free, compact, and abrasion-resistant pellets in both batch and continuous modes. With precise control over pellet output through air-classifying discharge, the process achieves a narrow particle size distribution and creates micro-pellets (100–400 µm) containing up to 95% active substance, solidifying the Wurster process as a top-tier solution for controlled release applications [Figure 4].

Cryo-pelletization

Liquid nitrogen cools formulations, such as solutions and emulsions at -160°C to create pellets, enabling quick freezing through efficient heat exchange. This method allows precise control over production based on temperature and solid

content. Conventional freeze-drying techniques then remove water or solvents from the frozen pellets.[23,24]

Freeze pelletization

In the freeze pelletization method, molten droplets of a solid are introduced into a column filled with an inert liquid. As these droplets travel through the column, they gradually solidify into spherical pellets. Their movement depends on their density relative to the liquid: Lighter droplets rise and are sprayed from the top, forming pellets at the bottom, while heavier droplets sink and are released from the bottom, solidifying at the top.

Spray congealing and spray drying

Spray congealing and drying are processes that produce uniform, spherical pellet particles by spraying hot melts, solutions, or suspensions. These methods can create small, consistent particles quickly by ensuring rapid evaporation or solidification. In spray drying, drug molecules in suspension or solution are atomized with inert excipients into hot air, causing the solvent to evaporate. As the droplets' viscosity increases, they form solid pellet particles, which are typically spherical and may have a porous structure.[20,21]

CHARACTERIZATION OF PELLETS[25-32]

Pellets require quality evaluation to ensure suitability and endurance during fill-up, during transport, and handling operations.

The physical attributes that are most commonly evaluated include:

Pellet size and size distribution

Pellet size is measured using sieve analysis, microscopy techniques, such as scanning electron microscopy (SEM), and laser diffraction. Pellet characteristics significantly impact the coating process and drug release rate. An alternative measurement method estimates fret diameter from four angles. Pellet shape affects flow during coating and filling into capsules. The ring gap analyzer is commonly used, alongside SEM for quantitative and qualitative assessment. Visual examination with various microscopes also aids in determining pellet shape.

Micromeritics

Tap density and bulk density affect the final product's strength, mixing separation, and batch variability. Bulk density is calculated by dividing the weight of a material by its volume, allowing for an accurate density assessment. This measurement can be done using an automated tapper or a pycnometer.

Table 2: Various advantages, disadvantage and recent improvements of pharmaceutical pellets

Advantages of pellets[5]	Disadvantages of pellets[13]
a. It enables combining several drug release rates in a unit dosage form b. Allow it to be freely dispersed throughout the GI and constantly optimize the absorption of drugs c. Lower the rate of stomach emptying to reduce variation in plasma profiles between and among subjects d. Pellets are the perfect shape for applying film coatings due to the low surface area-to-volume ratio e. The components of pellets remain stable and do not segregate during transportation	a. Measure medication by volume, not counting, and split it into single doses for accuracy and ease of use b. Involves either tab letting, which destroys the pellets' film coverings, or capsule filling, which raises costs c. The size of pellets can differ based on the formulation, typically ranging from 1 mm to 2 mm d. Producing pellets can be costly and necessitates skilled personnel and specialized equipment
Advantageous characteristics of pellets[14]	**Recent improvements using pellets[15]**
a. Pellets without coating b. A uniform sphere of spheres c. The same size d. Good qualities of flow e. Repeatable Packing f. Great power g. Low dust and low friability h. A level surface i. Coating ease	a. Multiple-unit dosage form combining immediate release and extended or sustained release b. As a pellet dose form that masks taste c. As a pellet that emulsifies itself d. Pellets based on pectin film coated for site-specific target delivery • Gastro retentive floating pellets. e. Pellets in the mouth that melt quickly f. A tablet with micro pellets.

Flowability

Flowability is assessed using the angle of repose. A value of $\Theta < 25°$ indicates excellent flowability, while a value of $\Theta > 40°$ signifies poor flowability.

Table 3: Various types of pellets technologies used for pharmaceutical dosage forms and their applications

Company	Pellets technology	Inference	Pharmaceutical applications
Elan	SODAS®	Spheroidal oral drug absorption system, multi-layered pellet	Avinza® Focalin®XR Luvox®CR
	PRODAS®	Programmable oral drug absorption system, SR mini tablets	Controlled release
Glatt	ZRx™	Uncoated pellets embodied in a tablet matrix	Customized SR applications
Supernus	Microtrol®	Multiparticulate system	AdderallSupernus® Equetro (Carbamazepine)
Andrx Pharm. (Watson)	Peltab System	Polymer coated pellets	Controlled release

Table 4: Pharmaceutical-marketed products of pellets are used in the treatment of diseases

Brand name	Drug	Company name	Use in diseases
Minocin capsules	Minocycline dihydrochloride	Triax Pharmaceutical's LLC	Bacterial infections
Inderal LA capsules	Propranolol hydrochloride	Wyeth Pharmaceuticals	Antihypertensive
Prilosec	Omeprazole	AstraZeneca Pharmaceuticals LP	Duodenal/Gastric Ulcer
Astrix capsules	Acetylsalicylic acid	Mayne pharma	Anti-inflammation/headache/ muscle aches
Sporanox capsule	Itraconazole	Janssen pharms	Antifungal
Tolsura capsule	Itraconazole	Mayne pharma	Antifungal
Talicia	Amoxicilline/omeprazole/Rifabutin	Redhill pharma	Bacterial infections
Focaline-XR	Dexmethylphenidate	Novartis	Attention deficit hyperactivity disorder

In vitro dissolution testing

In vitro dissolution testing is reliable for evaluating medication release behavior. It uses specialized equipment (USP I and USP II) that operates at different speeds (50/75/100 RPM) to simulate physiological conditions. The test is conducted using 900 mL of dissolution media.

Hardness and friability

Assessing the hardness of pellets is essential, as they must endure handling, shipping, storage, and coating processes. The Kaul Pellets Hardness Tester is utilized to measure relative hardness.

Kinetics of drug release

The drug release pattern in pellet formulations was examined using several kinetic models, including zero-order kinetics, first-order kinetics, Higuchi, Hixon-Crowell, Korsmeyer's, and Pappas equations. The correlation coefficient for each model was calculated, and the model with the highest correlation coefficient was chosen as the best-fit model for describing the drug release kinetics.

MECHANISM OF DRUG RELEASE FROM PELLETS

Drug release from pellets can occur through various mechanisms, including the following pathways:

Erosion

The outer layer of the pellet wears away, allowing drug release.

Osmosis

The phenomenon of osmosis is a powerful tool in drug delivery. Allowing water to enter under specific conditions builds up an osmotic pressure within the particle's interior, which forces the drug out through the coating and into the surrounding environment. This process has been extensively studied and proven to be highly effective in delivering drugs to their intended targets.

Diffusion

The active pharmaceutical ingredient molecule moves from the pellet matrix into the surrounding environment.

Table 5: Various pharmaceutical pellets, methods of preparations, and their purposes

Drug	Polymer	Method	Title	Inference
Nimodipine	Chitosan, MCC, mannitol, (SDS), crospovidone and CCS (Ac-Di-Sol)	extrusion-Spheronization	Preparation of sustained-release pellets of poorly soluble drugs by Co-grinding and extrusion-Spheronization[12]	Dissolution increased up to 240 min
Ibuprofen	Ethyl cellulose/ HPMC	Pelletization	Dual-component delivery system containing ibuprofen.[13]	From Core, drug release times from 16 to 24 h
Tamsulosin	Eudragit RSPO, Ethyl cellulose and HPMC	Pelletization	Formulation and evaluation of sustained release matrix tablet[14]	From the core tablet drug release time up to 12 h
Ibuprofen	Gelucire 50/13 (GL)	Melt solidification technique	Formulation and characterization of Gelucire pellets for sustained release of ibuprofen[15]	Drug was released in a sustained manner up to 8 h
Ketoprofen	Waxy maltodextrin and cremophor RH 40	Melt pelletization technique	An oral controlled-release matrix pellet formulation containing Nano-crystalline Ketoprofen[16]	Resulted SR Nano-crystalline ketoprofen from the matrix pellet
Metformin HCl	Eudragit L30D-55 and eudragit NE30D	Centrifugal granulation	Preparation and evaluation of SR Metformin HCl pellets[17]	Bioavailability and prolonged release effect increased
HCTZ and piroxicam	HPMC and starch	Extrusion/spheronisation	Immediate release of poorly soluble drugs from starch-based pellets prepared through extrusion/ spheronisation[18]	More than 80% of HCTZ and piroxicam were released in 30 min
Diclofenac Sodium	Carbopol 71G	Pelletization	Evaluation of diclofenac sodium release from matrix pellets compressed into MUPS tablets[19]	Drug release up to 8 h to complete dissolution released
Budesonide	Eudragit NE30D, L30D55 and FS30	Extrusion-spheronization	Development and evaluation of a novel pellet-based tablet system for potential colon delivery of budesonide[20]	Budesonide was released up to 24-h period
Budesonide	Eudragit S100	Extrusion-spheronization	Formulation and evaluation of sustained release enteric-coated pellets of Budesonide for intestinal delivery[21]	Drug is released in the stomach and then in the intestinal pH for 12 h
Budesonide	Eudragit E100 and FS30D	Extrusion-spheronization	Development of novel Budesonide pellets based on CODES technology: *In vitro/ in vivo* evaluation in induced colitis in rats[22]	Release rate was controlled in the buffer of pH 6.8 by the type and amount of polysaccharide
Borneol	Eudragit L30D-55, Eudragit L100 and Eudragit S100	Bottom spray coating	Preparation of the traditional Chinese medicine compound recipe heart-protecting musk pH-dependent gradient-release pellets[23]	PH-dependent gradient sustained release at pH of GI tract
Norfloxacin	HPMC K15M and eudragit RL 100	Extrusion-spheronization	Development and Optimization of a floating multiparticulate drug delivery system for norfloxacin[24]	The polymer coat shows sustained release of up to 8 h of the drug

(Contd...)

Table 5: *(Continued)*

Drug	Polymer	Method	Title	Inference
Diclofenac	Eudragit RS100 and Eudragit L100	Extrusion-spheronization	Biopharmaceutical Process of Diclofenac Multi-particulate Systems for Chronotherapy of Rheumatoid Arthritis[25]	Pulsatile-release pellets followed zero-order kinetics up to 18 h
Propranolol hydrochloride	Eudragit RS PO	Liqui-Pellet technology	Liqui-mass technology as a novel tool to produce sustained-release liqui-tablet made from liqui-pellets[26]	Sustain drug release from liqui-tablet formulation up to 24 h
Budesonide	Eudragit RS30D, Eudragit NE30D or surelease	Extrusion-spheronization	Pectin film coated pellets for colon-targeted delivery of budesonide: *In vitro/in vivo* evaluation in induced ulcerative colitis in rat[27]	Optimized formulation shows control delivery of Budesonide in the colon up to 18 h
5-fluorouracil	Ethyl cellulose or surelease	Extrusion-spheronization	Pectin/Ethyl cellulose as film coatings for colon-specific drug delivery: preparation and *in vitro* evaluation using 5-fluorouracil pellets[28]	Fluorouracil drug targeted delivery to the colon for up to 24 h
Rifampicin and isoniazid	Eudragit L-100	Extrusion-spheronization	Formulation and evaluation of enteric of rifampicin and isoniazid with improved rifampicin stability[29]	Rifampicin release was found to be 89% in formulation
Aceclofenac	EC N50 and HPMC E5	Fluid bed processor	Design and evaluation of sustained-release pellets of Aceclofenac[30]	Drug release of SR pellets lasted up to 28 h. in pH 6.8 PB
Mesalamine	Eudragit RSPO, Eudragit RL PO and Eudragit L100	Fluid bed processor	Design, development, and characterization of extended-release multiunit particulate system of anti-inflammatory drug[31]	Mesalamine pellets are released into the lower part of the intestine
Gliclazide	Ethyl cellulose and HPMC	Fluid bed processor	Development and evaluation of *in vitro* release kinetics of sustained release pellets of gliclazide using combinations of cellulose polymers[32]	The SR drug release in pH 7.4 or 7.5 over the duration of up to 8 h
Disopyramide phosphate	Eudragit L100 and S100	Extrusion-spheronization	Development and evaluation of porous membrane pellets of disopyramide phosphate for sustained release[33]	The prolonged drug release is up to 12 h

PHARMACEUTICAL APPLICATIONS OF PELLETIZATION TECHNOLOGIES

The application of various types of pelletization technologies used in pharmaceutical industries is summarized in Table 3.[6-13]

PHARMACEUTICAL MARKETED PELLETS PRODUCTS

Numerous pellet-based products are currently available in the pharmaceutical market and are used for treating a variety of diseases, as tabulated in Table 4.

PHARMACEUTICAL PELLETS, METHODS OF PREPARATIONS, AND THEIR PURPOSES[12-37]

Pharmaceutical pellets, method, polymer used for pellets and their application are showed in Table 5.

PHARMACEUTICAL PATENTS FOR PELLETS DOSAGE FORMS

The researchers have patents on pellets, summarized in Table 6.[34-45]

Table 6: Various pharmaceutical pellets drugs product patents along with their applications

Patent number	Title	Drug used	Purpose
US5958458	Pharmaceutical MUPS formulations in the form of coated cores[34]	Theophylline	Treatment of asthma
WO2004091583	Time-controlled release formulations and atrial fibrillation treatment method[35]	Diltiazem	Antihypertensive
US2004048814	Sustained release composition containing clarithromycin[36]	Clarithromycin	Antibacterial
US6984402	Formulations of Chrono delivery and method of treating atrial fibrillation[37]	Methylphenidate	Attention deficit hyperactivity disorder
WO2007011131	Stabilized controlled-release type pellet containing tolterodine[38]	Tolterodine	Antimuscarinics
WO2007138022	Lipoic Acid Granules[39]	Lipoic acid	Treating nerve pain caused by diabetes, reducing blood sugar levels.
WO2007073894	Oral preparation with controlled release[40]	Metoprolol	Antihypertensive
WO2008064734	Medicament with controlled release Galanthamine[41]	Galanthamine	Treatment in Alzheimer's disease
WO2009042778	Controlled release pharmaceutical composition[42]	Carbamazepine/ Mesalamine/ Propafenon	Anticonvulsant/treat ulcerative colitis/Treat arrhythmia
WO2001015668	Controlled release pellets formulations[43]	Verapamil	Antihypertensive
WO2002028376	Formulations of Chrono delivery and method of use thereof[44]	Diltiazem	Antihypertensive
WO2004002398	Spherical pellet containing a water-soluble active ingredient[45]	Tramadol	Analgesics

CONCLUSION

Pellets are the multi-unit's particulate dosage forms that offer dosage forms with improved safety and efficacy of the active pharmaceutical ingredients with excellent content uniformity in single-unit dosage forms. The pelletization technique produces uniform spherical pellets and offers more advantages in fabrication than other granulation processes. Today pelletization represents an efficient pathway for novel drug delivery in the scope for the development of different modified-release solid oral dosage forms.

AUTHORS CONTRIBUTIONS STATEMENT (CRediT FORMAT)

Vishal Gupta was involved in data collection, making of the writing-original draft, language, figures, and tables of the manuscript. Jitendra Gupta was in charge of the conceptualization, reviewing, and editing of the manuscript.

ACKNOWLEDGMENT

Authors thank to the management of the Institute of Pharmaceutical Research, GLA University, Mathura, U. P., India.

REFERENCES

1. He W, Du Q, Cao DY, Xiang B, Fan LF. Study on colon-specific pectin/ethylcellulose film-coated 5-fluorouracil pellets in rats. Int J Pharm 2008;348:35-45.
2. Ross JA, Kasum CM, Davies SM, Jacobs DR, Folsom AR, Potter JD. Diet and risk of leukemia in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2002;11:777-81.
3. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. Lancet 2007;370:59-67.
4. Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y, *et al*. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood 2013;122:2539-49.
5. Marcel D, Ghebre SI. Pharmaceutical Pelletization Technology. Vol. 58. New York: CRC Press; 1989. p. 600-78.
6. Tanaka C, Yin OQ, Sethuraman V, Smith T, Wang X, Grouss K, *et al*. Clinical pharmacokinetics of the BCR-ABL tyrosine kinase inhibitor nilotinib. Clin Pharmacol Ther 2010;87:197-203.
7. Tojo A, Usuki K, Urabe A, Maeda Y, Kobayashi Y, Jinnai I, *et al*. A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph^+

CML or relapsed/refractory Ph+ ALL. Int J Hematol 2009;89:679-88.
8. Donald LW. Hand Book of Pharmaceutical Controlled Release Technology. New York: Marcel Dekker, Inc.; 2005. p. 435-40.
9. Gwen MJ, Joseph RR. Sustained and controlled release drug delivery system. In: Modern Pharmaceutics. 3rd ed., Vol. 12. New York: Marcel Dekker, Inc.; 1996. p. 582-93.
10. Aegis K. Treatise On Controlled Drug Delivery. 1st ed. New York: Marcel Dekker, Inc.; 1992. p. 43-93.
11. Chien YW. Novel Drug Delivery System: Fundamentals, Development Concept, Biomedical Assessments. 1st ed., Vol. 56. New York: Marcel Dekker Inc.; 2001. p. 581-90.
12. Pan K, Xing T, Yang J. Preparation of sustained release pellets of poorly soluble drugs by cogrinding and extrusion-spheronisation. Asian J Pharm Sci 2009;4:106-14.
13. Lopes CM, Lobo JM, Pinto JF, Costa PC. Compressed matrix core tablet as a quick/slow dual-component delivery system containing ibuprofen. AAPS PharmSciTech 2007;8:E76.
14. Nithiyananthan TS, Shankarananth V, Rajasekhar KK, Hareesh G. Formulation and evaluation of tamsulosin hydrochloride as sustained release matrix tablet. Int J Chem Tech Res 2009;1:1278-90.
15. Fetih GN. Formulation and characterization of Gelucire pellets for sustained release of Ibuprofen. Bull Pharm Sci Assiut Univ 2010;33:217-24.
16. Vergote GJ, Vervaet C, Van Driessche I, Hoste S, De Smedt S, Demeester J, *et al*. An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen. Int J Pharm 2001;219:81-7.
17. Hu LD, Liu Y, Tang X, Zhang Q. Preparation and *in vitro*/*in vivo* evaluation of sustained-release metformin hydrochloride pellets. Eur J Pharm Biopharm 2006;64:185-92.
18. Dukić-Ott A, Remon JP, Foreman P, Vervaet C. Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/spheronisation. Eur J Pharm Biopharm 2007;67:715-24.
19. Ivić B, Ibrić S, Betz G, Djurić Z. Evaluation of diclofenac sodium release from matrix pellets compressed into MUPS tablets. Yakugaku Zasshi 2009;129:1375-84.
20. Varshosaz J, Emami J, Tavakoli N, Minaiyan M, Rahmani N, Dorkoosh F. Development and evaluation of a novel pellet-based tablet system for potential colon delivery of budesonide. J Drug Deliv 2012;2012:905191.
21. Raval MK, Ramani RV, Sheth NR. Formulation and evaluation of sustained release enteric-coated pellets of budesonide for intestinal delivery. Int J Pharm Investig 2013;3:203-11.
22. Varshosaz J, Emami J, Tavakoli N, Minaiyan M, Rahmani N, Dorkoosh F, *et al*. Development of novel budesonide pellets based on CODES(TM) technology: *In vitro*/*in vivo* evaluation in induced colitis in rats. Daru 2011;19:107-17.
23. Song H, Guo T, Zhang R, Zheng C, Ma Y, Li X, *et al*. Preparation of the traditional Chinese medicine compound recipe heart-protecting musk pH-dependent gradient-release pellets. Drug Dev Ind Pharm 2002;28:1261-73.
24. Salve V, Mishra R, Nandgude T. Development and optimization of a floating multiparticulate drug delivery system for norfloxacin. Turk J Pharm Sci 2019;16:326-34.
25. Battu S, Yalavarthi PR, Reddy GS, Radhakrishnan S, Thummaluru RM, Konde A. Biopharmaceutical process of diclofenac multi-particulate systems for chronotherapy of rheumatoid arthritis. Turk J Pharm Sci 2018;15:256-62.
26. Lam M, Nashed N, Nokhodchi A. Liqui-mass technology as a novel tool to produce sustained release liqui-tablet made from liqui-pellets. Pharmaceutics 2021;13:1049.
27. Varshosaz J, Emami J, Tavakoli N, Minaiyan M, Rahmani N, Dorkoosh F, *et al*. Pectin film coated pellets for colon-targeted delivery of budesonide: *In-vitro*/*in-vivo* evaluation in induced ulcerative colitis in rat. Iran J Pharm Res 2012;11:733-45.
28. Wei H, Qing D, De-Ying C, Bai X, Fanli-Fang. Pectin/ethylcellulose as film coatings for colon-specific drug delivery: Preparation and *in vitro* evaluation using 5-fluorouracil pellets. PDA J Pharm Sci Technol 2007;61:121-30.
29. Krishna TV, Reddy MS. Formulation and evaluation ofenteric coated pellets of rifampicin and isoniazid with improved rifampicin stability. Asian J Pharm Clin Res 2014;7:154-6.
30. Ravella VN, Nadendla RR, Kesari NC. Design and evaluation of sustained release pellets of aceclofenac. J Pharm Res 2013;6(5):525-31.
31. Daslaniya D, Patel MP, Shah A. Design, development and characterization of extended release multiunit particulate system of anti-inflammatory drug. Int J Pharm Sci Drug Res 2009;1:100-2.
32. Sultana S, Khpsru KH, Masud AA. Development and evaluation of *in vitro* release kinetics of sustained release pellets of gliclazide using combinations of cellulose polymers. J Pharm Educ Res 2012;3:1-9.
33. Bathool A, Gowda DV, Khan, MS. Development and evaluation of porous membrane pellets of disopyramide phosphate for sustained release. Asian J Pharm 2012;6:107-15.
34. Norling T, Jensen LN, Hansen J. Pharmaceutical Multiple Unit Particulate Formulation in the Form of Coated Cores. US5958458; 1999. Available from: https://patents.google.com/patent/US5958458A/en [Last accessed on 2024 Sep 12].
35. Mehta AM. Chrono Delivery Formulations and Method of Use Thereof. WO2004091583; 2004. Available from: https://patents.google.com/patent/US6926909B2/en [Last accessed on 2024 Sep 12].
36. Vanderbist F, Sereno A, Baudier P. Sustained Release Composition Containing Clarithromycin.

US2004048814; 2004. Available from: https://patents.google.com/patent/WO2001049246A2/en [Last accessed on 2024 Sep 13].
37. Mehta AM. Chrono Delivery Formulations and Method of Treating Atrial Fibrillation. US6984402; 2006. Available from: https://patents.google.com/patent/US6926909B2/en [Last accessed on 2024 Sep 13].
38. Shin HJ, Lim JL, Nam KK. Stable Controlled-release Pellet Containing Tolterodine. WO2007011131; 2007. Available from: https://patents.google.com/patent/WO2007011131 [Last accessed on 2024 Sep 13].
39. Boltri L, Fabiani F, Mapelli L, Salvi A, Magri P, Nardi A, *et al.* Lipoic Acid Pellets. WO2007138022; 2007. Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2007138022 [Last accessed on 2024 Sep 13].
40. Schlütermann B, Kohlmeyer M. Oral Preparation with Controlled Release. PCT Patent Application WO2007073894 A3. Available from: https://data.epo.org/gpi/ep1965775b1-oral-preparation-with-controlled-release [Last accessed on 2024 Sep 14].
41. Alles R, Muskulus F, Bruck S, Schulze NJ. Medicament with Controlled Release Containing Galanthamine. WO2008064734; 2008. Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2008064734 [Last accessed on 2024 Sep 14].
42. Sen H, Jayanthi SK, Raghavan V, Arra GS. A Controlled Release Pharmaceutical Composition and A Process for Preparing the Same. WO2005048978A2; 2005. Available from: https://patents.google.com/patent/WO2005048978A2/zh [Last accessed on 2024 Sep 14].
43. Mulye N. Controlled Release Pellet Formulation. WO2001015668; 2001. Available from: https://patents.google.com/patent/WO2001015668A1/en [Last accessed on 2024 Sep 14].
44. Remon JP, Debunne A. Controlled Release Pharmaceutical Pellet, Compositions for Reducing Side Effects of Drug. WO2002028376; 2002. Available from: https://patents.google.com/patent/WO2002017877A2/en [Last accessed on 2024 Sep 15].
45. Strong B, Kloemkes M, Bachmann D. Spherical Pellet Containing A Water Soluble Active Ingredient. WO2004002398; 2004. Available from: https://patents.google.com/patent/EP1519704A2/en [Last accessed on 2024 Sep 15].

Source of Support: Nil. **Conflicts of Interest:** None declared.