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A review on miracles of Pelletization technique in delivery of drugs and their future Perspectives

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ABSTRACT

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. As for dosage form miracles, advanced technologies enable novel drug delivery systems, allowing for precise dosing, targeted delivery and improved bioavailability, leading to breakthroughs in treating previously challenging diseases. One key of pellet dosage forms lies in their ability to enable controlled and sustained drug release, leading to enhanced therapeutic efficacy, and reduced side effects. Ultimately technologies contribute to improved patient outcomes and quality of life. Moreover, integrating nanotechnology and biodegradable polymers is anticipated to revolutionize the design of pellets, enabling precise control over drug release kinetics and enhancing therapeutic efficacy.

Keywords: Pelletization, Pellets, Pellets technologies, pellets marketed products, Patent in pellets

INTRODUCTION:

Pelletization can be defined as an agglomeration process that converts fine powders or particles of a bulk drug and excipients into small, free-flowing, more or less spherical units, called pellets

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or hemispherical solid units typically from about 0.5- 2mm.

These are intended usually for oral administration. These are spheres of varying diameter depending on the application and the wish of the producer.

Applications are found not only in the pharmaceutical industry but also in agribusiness (e.g., fertilizer, fish food) and the polymer industry [1-3].

In the pharmaceutical industry pellets can be defined as a small free flowing spherical particulate manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. Traditionally, the word pellet has been used to describe a variety of systematically

produced geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions.

In at early phase of 1950's it was came in pharmaceutical industry to get response of sustained release or extended release of drugs in formulations.

Pellets are prepared using different technologies such as layering of the drug solution, suspension or powder on the inactive cores, extrusion, Spheronization and agglomeration in roto-granulators or rot processors, compression, spray drying and spray congealing.

The recent novel trends of pellets are;

1. They help in preparation of modified release multiple dosage form with different release patterns like immediate and sustained release pattern.
2. They help in taste masking of the drugs which are bitter in taste.
3. They are available as mouth melt pellets.
4. Polymer based pellets for control release pattern of drug.
5. As fast dissolving tablets containing micro pellets.
6. As a self-emulsifying pellets.
7. Gastro retentive floating pellets etc.

This trend of pellets has increased patient acceptance. This novel trend helps in giving the information about the releasing pattern of the drug and its bioavailability of the drug to the systemic circulation of the and how it as increased the patient acceptance of pH sensitive drugs releasing pattern of drugs, taste mask of the drugs, self-emulsification of pellets, and polymer based control release of the drugs, mouth melt pellets etc.

Pellet formation and growth:

The mechanism of pellet formation and growth, the following steps were proposed:

(1) Nucleation

(2) Coalescence

(3) Layering

(4) Abrasion transfer.

(1) Nucleation: Nucleation is a common stage in all Pelletization/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three phase air wetted liquid nuclei and are attached together by liquid bridges, which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of primary particles, moisture content, viscosity of binding particles, wet ability of substrate and the processing conditions, such as tumbling and drying rates, influence the size, rate and the extent of nuclear formation. Both mass and number of nuclei in the system changes as a function of time, this is an important feature of nucleation. Nucleation followed by a transition phase and the growth mechanism affecting the transition region are coalescence and layering.

(2) Coalescence: Coalescence is defined as the formation of large sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering is

a slow growth mechanism and involves a successive addition of fragments and fines on an already formed nucleus.

(3) Layering: In the layering step, the number of particles remains same but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction that occurs due to attrition, breakage and shatter. The fines and fragments that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favorable coalition's declines rapidly, thereby leading to a reduction in the rate of growth of the pellets.

(4) Abrasion transfer: In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of material from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles however undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

Advantages of Pellets [3-8]:

- Flexibility in dosage form design and development
- It permits the combination of different release rates of the same drug in a single dosage form
- Controlled release technology
- Disperse freely in the GI& invariably maximize drug absorption
- Reduce peak plasma fluctuation
- Minimize potential side effects without lowering bioavailability
- Avoiding high local concentration
- Less susceptible dose dumping
- Reduce gastric emptying rates so minimize inter and intra subject variability of plasma profile
- Pellets have a low surface area to volume ratio and provide an ideal shape for application of film coatings
- Reproducible fill weights in capsules
- Can be used to mix incompatible drugs.
- Pellets are non-dusting.
- The ingredients that make up a pellet do not separate during transit and storage.
- Pellets also allow the separation of incompatible ingredients with in different layers of the pellet body. Pellets also allow the separation of incompatible ingredients with in different layers of the pellet body.
- Pellets over comes the problems occurred my conventional tablets and crushed tablets.
- The pellets are used to mask the taste of the bitter drugs
- Coated pellets are used to produce the sustain release of drug and also increases the patient acceptance.
- Pellets are easily dispersed in the G.I.T. due to their small size and have a large surface area of absorption and reduce the peak plasma level fluctuations.
- A pellet reduces the gastric emptying rate and intestinal transit time thus reduces the intra and inters subject variability.

Disadvantages of Pellets [13]:

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tab letting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1to 2mm.
- Preparation of pellets is quite expensive and required qualified persons and specialized equipment's.

Desirable properties of Pellets [14, 15]:

- Uncoated pellets.
- Uniform spherical shape.
- Uniform size.
- Good flow properties.
- Reproducible packing.
- High strength.
- Low friability, low dust.
- Smooth surface.
- Ease of coating.

Recent advancement of Pellets:

Pellets have the novel approaches; they are:

1. Multiple unit dosage form by the combination of;
    (a) immediate release
    (b) sustained release
2. As taste masking dosage form of pellets.
3. As a self-emulsifying pellets
4. Pectin film coated based pellets for site specific target delivery.
    (a) Gastro retentive floating pellets.
5. Fast melting pellets in mouth.
6. Micro pellets in a tablet.

Once coated:

- Maintain all of the above properties,
- Have desired drug release characteristics.

List of Pelletization Techniques or processes [16]:

1. Extrusion-Spheronization Technique
    (a) Solvents free cold Extrusion-Spheronization
    (b) Extrusion-Spheronization via melt technology
2. Drug-Layering technology
    (a) Powder-solvent layering technique
    (b) Suspension/solution layering technique
    (c) Dry-Powder layering technique

3. Spray granulation
4. Cryo-pelltization
5. Freeze Pelletization
6. Spray drying and spray congealing

(1) Extrusion-Spheronization Technique:

Extrusion-Spheronization are most common multistep process in which Pellets can be produce with high loading content of active ingredient of uniform size and with own good flow properties.

Principles for Extrusion-Spheronization technique are as follows-
a) **Dry Mixing-**Dry mixing of ingredients is done to achieve homogenous powder dispersion using Twin shell blender, planetary mixer, High speed mixer and Tumbler mixer.
b) **Wet massing-**It is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and process as employed in wet granulation for compaction.

Brief technique process is as follows:
Extrusion- In this process wet mass pressurized and passes through a optimized or validated openings of die plate screen to produces rod or cylindrical shaped particles of uniform diameter with enough plasticity and mechanical strength. Such shaping of wet mass into long cylindrical rods, commonly termed as 'extrudes'.

Spheronization-It is also known as 'Merumerizer' i.e formation of spherical uniform sized pellets particle. its consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces (Fig.2). Two geometric patterns are generally used. It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the centre of the disc.

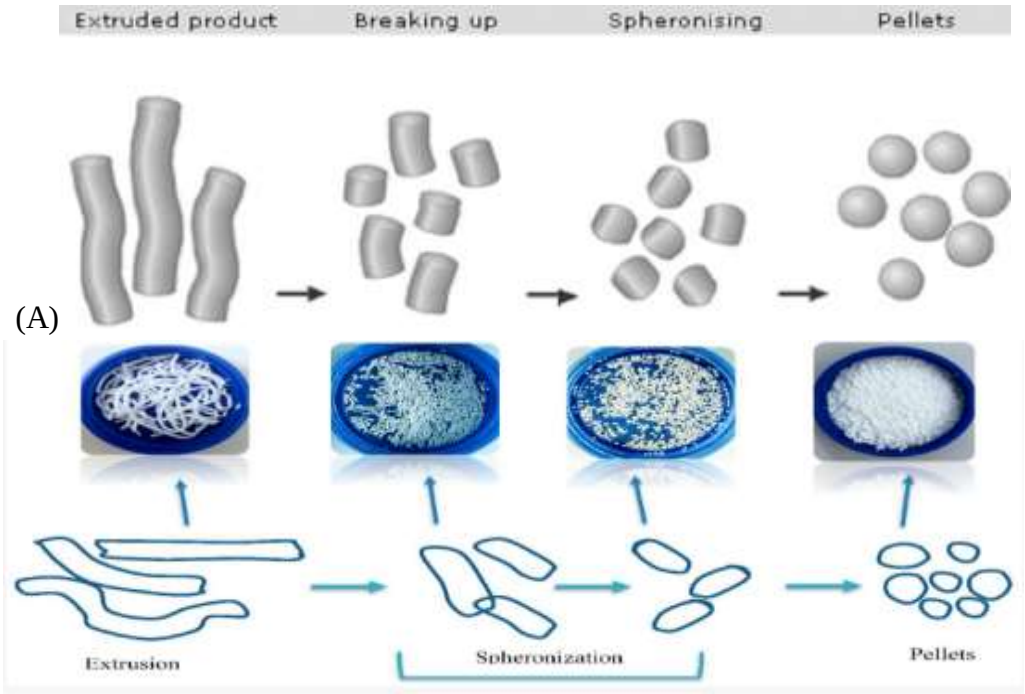

Figure 1(A&B): Spheronization & Extrusion process to form pellets.

Solvent Free Cold Extrusion-Spheronization:

The process was introduced by Breitkreutz *et al.* [17, 18] in 2003, for the production of taste masked paediatric formulations. Solvent free cold extrusion has proceeded from hot-melt processes but it does not utilize high temperatures in process. It comprises the steps of mixing the active ingredient with a lipid binder composition comprising at least a glycerol type hard fat, cold extruding the mixture and spheronizing the extrudate to obtain pellets or spherical granules. An additional attribute of these pellets is the formation of a taste masking lipid layer on their surface during the Spheronization step.

Extrusion-Spheronization via melt technology

It is process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the more uniform dispersion.

(2) Drug-Layering technology:

It includes successive layers deposition of drug molecules from the solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or Non-Pareil Seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder drug layering, a binder solution is first sprayed onto previously prepared inert seeds, followed by the addition of powder.

(a) **Powder-solvent layering technique:** In powder layering liquid saturation is low and irrespective of the solubility of the drug in the binding liquid, complete dissolution does not occur. Typically, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The most nuclei tumble in the rotating pan of disc, pick up powder particles, and form layers of small particles that adhere to each other and the nuclei by means of capillary forces developed in the liquid phase. As additional bonding, liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained. On drying, the binder and other dissolved substance crystallize out and the liquid bridges are partially replaced by solid bridges. On spraying with binder, fines may pick up moisture and enter a nucleate on phase (fig.3).

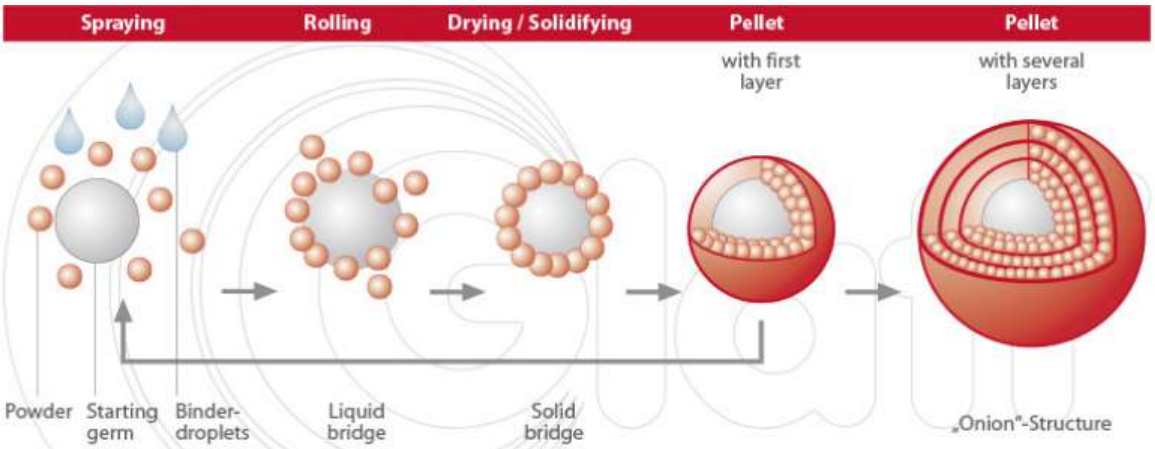

Figure.2 Diagrammatic representation of powder layering process.

(b) **Suspension/solution layering technique:**

The most popular process variant for constructing pellets is coating a core with a suspension or solution. By spraying on the layering fluid, an active substance layer with the desired amount of active ingredient can be achieved. In most cases, film coating follows the layering process. The quality of the coated pellets depends strongly on the quality of the prepared active substance pellet: round form, smooth surface, narrow particle

size distribution. The result re-rounds pellets with a dense structure and even surface. These – depending on the active substance utilized – can be enhanced for multiple product properties [19]. (fig.4)

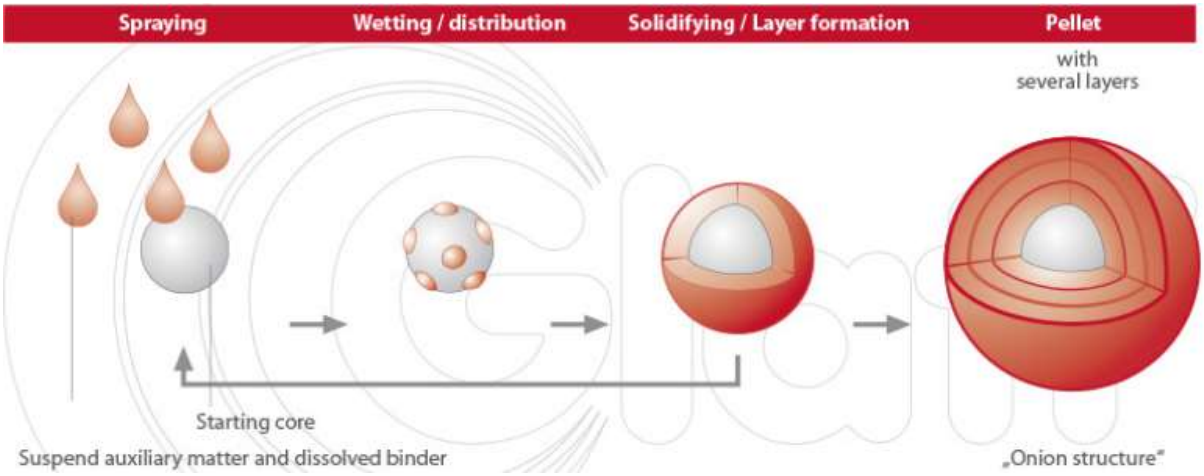

Figure.3 Diagrammatic representation of Suspension/solution layering technique

(c) **Dry-Powder layering technique:** It is most efficient solution for layered build-up of pellets in pharmaceutical industry process. Dry powder layering is a process for constructing active substance pellets by coating a starter core with an ingredient in powder form. This is done with the help of a binding solution fixed to the starter core. The advantage of this process compared to layering with liquid active substances is that the processing time is significantly reduced which leads to a higher efficiency. With optimal process settings, hourly weight gains of up to 300 percent are possible. For powder layering, we use the rotor process. The micro-fine substance is sucked into the processing chamber through a powder nozzle. The results are dust-free, very round active substance pellets with a narrow particle size distribution. Powder is mixed and moistened with a solvent or binder and the powder bed is set into a centrifugal motion (Fluid Bed Pelletizing in the rotor). The impact and acceleration forces that occur in this process result in the formation of agglomerates, which become rounded out into uniform and dense pellets. The speed of rotation has a direct influence on density and size of the pellets. The moist pellets are subsequently dried in the fluid bed [22].

(3) **Spray granulation technique:** This process is particularly suitable for a controlled release of active ingredients. In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate (fig. 5). They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated. Fluidized bed spray granulation enables the manufacture of round, dust-free, compact and abrasion resistant pellets from liquids. Spherical granulate can be manufactured in the batch or continuous operation mode of a fluidized bed system. Particularly narrow particle size distribution and outstanding pellet roundness are achieved by controlling the pellet output

using an air-classifying discharge. Using this method, micro-pellets (100 to 400 micrometers) with an active substance content of up to 95 percent can be achieved.

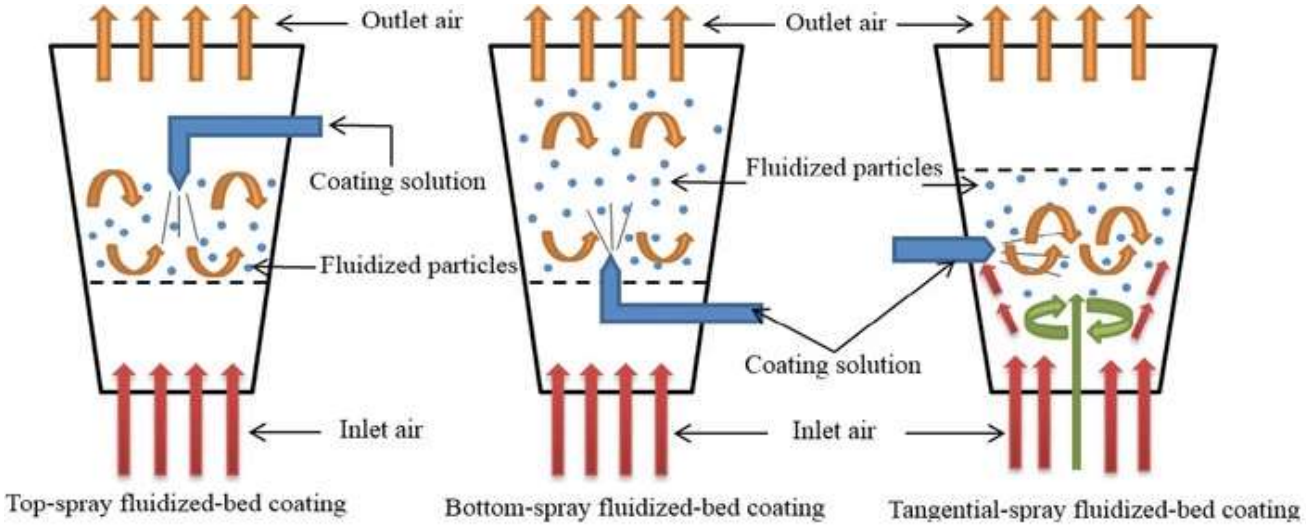

Figure.4 Diagrammatic representation of Spray granulation technique (top spray, bottom spray and tangential spray granulation)

(4) **Cryo-pelltization:** Pellets can be prepared by sprinkle droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160˚C in which liquid nitrogen used as solidifying medium. The procedure permits freezing of the material being processed due to rapid heat transfer that occurs between the droplets and liquid nitrogen for manufacturing a given quantity depends on the solid content and temperature of solution, solvent or suspension being processed. Conventional freeze dryers are used to the escape water or organic solvents from the medium i.e. pellets.[23-24]

(5) **Freeze Pelletization:** In Freeze Pelletization technique, a solid medium in molten stage is uses as droplets and introduced into an inert column of liquid in which the molten solid is immiscible. The molten solid moves in the liquid column as droplets and solidifies into spherical pellets. Depending on the density of droplets the molten solid droplets can move upward or downward in the liquid column with respect to the liquid in the column. If the density of the molten-solid medium is less than that of the liquid in the column, then droplets are introduced from top of the column and pellets solidify in the bottom portion of the column. Vice-versa, if the density of molten-solid medium is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and pellets solidify at the top portion of column.

(6) **Spray drying and Spray congealing:** spray drying [20] and spray congealing [21] both are globulation processes involve spraying of hot melts, solutions or suspensions to prepared uniform spherical particles of pellets. For producing small uniform size of pellets to kept high rate of evaporation or congealing. During spray drying, drug molecules in solution or suspension are sprayed with or without inert excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air evaporation of the appropriate medium is initiated. This drying process continues going to that stage whereby the viscosity of the droplets constantly increases until finally processing of medium is driven off and solid pellets particles sized are formed. Generally spray-dried pellets tend to be spherical, non uniform in size and porous in nature.

Characterization of Pellets [25-31]:

Pellets are evaluated for certain quality measures, which reflect the suitability and endurance of material during various operations like filling, transportation and handling.

The most common physical characteristics evaluated are:

1. **Pellet size and size distribution,** determined by sieve analysis which is simple and economical; microscopy methods like Scanning electron microscopy (SEM) and laser diffraction [33, 34]. This characteristic feature of pellets affects coating and rate of drug release. Another method to determine the size of pellets is estimation of fret diameter obtained from four different angles. In all cases, the size data was best fitted by a normal distribution.
2. **Shape** influences flow of pellets during coating, filling into capsules and dies. The most common method of analysis is by ring gap analyzer; scanning electron microscopy (SEM) for qualitative and quantitative analysis. Visual inspection of pellets by microscope and stereomicroscope also determine shape of pellets.
3. **Bulk Density and tap density** affects potency of finished product, produces segregation during mixing and leads batch to batch variation. The bulk density was calculated by the ratio of weight to the occupied volume and is measured by automated tapper or a pycnometer.
4. **Flowability** is determined by angle of repose. If $\Theta<30°$-excellent Flowability and $\Theta>40°$- poor flow ability.
5. **In-vitro Dissolution Testing** most commonly is by USP I (basket) and USP II (paddle) apparatus at a speed of 50/75/100 RPM in 900 ml of dissolution media to study the release pattern of the coated pellets.
6. **Hardness and friability** determination of pellets is evaluate necessary because the pellets having to withstand during handling, shipping, storage and during coating process. The relative hardness is calculated with the help of instrument Kaul pellets hardness tester.
7. **Tensile strength** of pellets is calculated by using tensile apparatus with a 5 kg load cell. The load is recorded and the tensile strength is calculated with the help of applying the value for the failure load and the radius of pellets.
8. **Stability study:** Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.
9. **Kinetics of Drug Release:** The dissolution profile of pellets formulation was fitted to zero order kinetics, first order kinetics, Higuchi, Hixon-Crowell, Korsmeyer's and Pappas equation to ascertain the kinetic modeling of drug release and the model with the higher correlation coefficient was considered to be the best fit model.

Mechanism of Drug Release from Pellets: The mechanism of drug release from pellets can occur in the following ways:

1. **Erosion:** Some coatings are designed to erode gradually with time, thereby releasing the drug contained within the particle.
2. **Osmosis:** In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.
3. **Diffusion*:*** On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Pharmaceutical pellets technologies and its applications:

The use of pellets technologies in the pharmaceutical industry has proven to be a significant advancement, facilitating the development of complex drug delivery systems that offer precise dosing, controlled release, and improved patient compliance. These technologies have revolutionized the formulation of medications, enabling the creation of personalized therapies and enhancing the bioavailability of active pharmaceutical ingredients. Moreover in table 1, the versatility of pellet technologies has extended to various fields, including agriculture and food processing, where they have contributed to efficient nutrient delivery and improved product stability. The miracle of pellets technologies lies in their ability to revolutionize drug delivery and product formulation across diverse sectors, thereby fostering innovation and addressing complex healthcare and agricultural challenges.

Table 1: Various types of pellets technologies used in Pharmaceutical 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
	IPDAS®	Tablet incorporating extruded spheronized multiparticulates	Naprelan
Glatt	ZRx™	Uncoated pellets embodied in a tablet matrix	Customized SR applications
Eurand (Reliant Pharm. LLC)	Diffucaps®	Multiparticulate bead system comprised of multiple layers of drug, excipients, and release-controlling polymers.	Innopran XL (Propranolol HCl) AMRIX (Cyclobenzaprine HCl ER Capsules)
	PULSYS™	Tableted multiparticulate system for pulsatile release	Moxatag™ sst (Amoxicillin)
Supernus	Microtrol®	Multiparticulate system	AdderallSupernus ® Equetro (Carbamazepine)
	Avert®	Matrix multiparticulate	Reduced abuse potential for dosage forms

Andrx Pharm. (Watson)	Peltab System	Polymer coated pellets	Controlled release
	PPDS	Pulsatile drug delivery system	Controlled release
	Multipart®	Tableted multiparticulate system for pulsatile release	Pulsatile release

Pharmaceutical pellets formulation and its markets products:

Current marketed pellet dosage forms is expected to involve advancements in personalized medicine, targeted drug delivery systems, and enhanced patient compliance. This includes the development of innovative technologies for site-specific drug release, incorporation of nanotechnology for improved bioavailability, and the utilization of functional coatings to achieve specific therapeutic objectives. Additionally, there is an increasing focus on the development of multifunctional pellets that combine different drugs or active ingredients to address complex medical conditions, thereby streamlining treatment regimens and enhancing therapeutic outcomes, Table 2.

Table 2: Various pellets pharmaceutical product used in Treatment

S.no	Brand name	Drug	Formulation type	Company name	Use in Treatment
1	Minocin Capsules	Minocycline Dihydrochloride	Pellets	Triax Pharmaceutical's LLC	Bacterial infections
2	Inderal LA Capsules	Propranolol hydrochloride.	Pellets	Wyeth Pharmaceuticals	Antihypertensive
3	Testopel	Testosterone	Pellets	Slate Pharma	Hypogonadism
4	Prilosac	Omeprazole	Pellets	AstraZeneca Pharmaceuticals LP	Duodenal/ Gastric Ulcer/ Gastroesophageal Reflux Disease
5	Astrix Capsules	Acetylsalicylic acid	pellets	Mayne pharma	Anti inflammation/head ache/muscle aches
6	Doryx Capsules	Doxycyline	pellets	Mayne pharma	Bacterial infections
7	Sporanox capsule	Itraconazole	Pellets	JANSSEN PHARMS	Antifungal
8	Tolsura capsule	Itraconazole	Pellets	Mayne pharma	Antifungal
9	Talicia	Amoxicilline/omeprazole magnesium/Rifabutin	Pellets	Redhill Pharma	Bacterial infections
10	zegerid	Omeprazole/sodium bicarbonate	Pellets	Salix Pharma	Gastroesophageal Reflux Disease
11	Bontril	Phendimetrazine Tartrate	pellets	Valeant Pharma	CNS stimulants

12	Toprol-XL	Metoprolol succinate	Pellets	TOPROL Pharma	Antihypertensive
13	Focaline-XR	Dexmethylphenidate	Pellets	NOVARTIS	Attention deficit hyperactivity disorder (ADHD)
14	Lyrica CR	Pregabalin	Pellets	UPJOHN pharma	Anti-epileptic
15	Cardizem CD	Diltiazem Hydrochloride	Pellets	Bausch Pharma	Anti hypertensive
16	Tiazac	Diltiazem Hydrochloride	Pellets	Bausch Pharma	Anti hypertensive
17	Dilgard XL 180	Diltiazem Hydrochloride	Pellets	Smith Kline and French	Anti hypertensive
18	Procomp	Prochlorperazine Maleate	Pellets	Jubilant Cadista	Antipsychotic/Schizophrenia
19	Innopran XL	Propranolol hydrochloride	Pellets	Ani Pharms	Antihypertensive
20	Apriso	Mesalamine hydrochloride	Pellets	Valeant Pharms Intl	Ulcerative colitis
21	Pentasa	Mesalamine hydrochloride	Pellets	Takeda Pharms Usa	Ulcerative colitis
22	Flomax	Tamsulosin HCl	Pellets	Sanofi	Benign prostate enlargement
23	Jalyn	Tamsulosin HCl	Pellets	Woodward	Benign prostate enlargement
24	Prevpac	Amoxicillin; Clarithromycin; Lansoprazole	Pellets	Takeda Pharms Usa	Bacterial infections
25	Dexilant	Dexlansoprazole	Pellets	Takeda Pharms Usa	Zollinger–Ellison syndrome/ Gastroesophageal Reflux Disease
26	Prevacid	Lansoprazole	Pellets	Takeda Pharms Usa	Gastroesophageal Reflux Disease
27	Detrol LA	Tolterodine Tartrate	pellets	Upjohn	overactive bladder
28	Entocort EC	Budesonide	Pellets	Padagis US	Wheezing and shortness of breath
29	Norpace CR	Disopyramide Phosphate	pellets	Pfizer	Antiarrhythmic
30	Verelan PM	Verapamil Hydrochloride	Pellets	Recro Gainesville	Antihypertensive

Pharmaceutical pellets method of preparation and used in dosage forms:

Pellets as a dosage form offer several advantages, including improved drug stability, controlled release, and reduced gastrointestinal irritation. These can be used for various purposes such as sustained or controlled drug

delivery, multiple drug therapy, and combination therapies. The pellets can be formulated into different forms, including immediate-release pellets, delayed-release pellets, extended-release pellets, and enteric-coated pellets, catering to different therapeutic needs, table 3. They are often employed in the pharmaceutical industry for the development of oral solid dosage forms, allowing for flexibility in drug release profiles and improving patient compliance.

Table 3: Various pellets method of preparation used in pellets dosages forms

S.no	DRUG	POLYMER	METHOD	TITLE	INFERENCE
1	Nimodipine (NMD)	Chitosan, MCC, mannitol, (SDS), crospovidone and CCS (Ac-Di-Sol)	Co-grinding and extrusion-spheronization	Preparation of sustained release pellets of poorly soluble drugs by Cogrinding and extrusion-spheronization[32]	The mixture increased dissolution rate of NMD up to 240 min.
2	Ibuprofen	Ethyl cellulose/ Hydroxy propyl methyl cellulose	Pelletization	Dual-component delivery system containing ibuprofen[33]	Drug in the core tablet was released at different times (approx.16 or 24 hours)
3	Tamsulosin	Eudragit RSPO, Ethyl cellulose and Hydroxy propyl methyl cellulose	Pelletization	Formulation and evaluation of sustained release matrix tablet[34]	Drug in the core tablet was released at different times up to 12 hrs.
4	Ibuprofen	Gelucire 50/13 (GL)	Melt Solidification Technique	Formulation and characterization of Gelucire pellets for sustained release of ibuprofen[35]	Drug was released in a sustained manner up to 8 hrs.
5	Ketoprofen	Waxy maltodextrin and Cremophor RH 40	Melt Pelletization technique	An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen[36]	Resulted SR Nano-crystalline ketoprofen from the matrix pellet formulations
6	Metformin hydrochloride	Eudragit L30D-55 and Eudragit NE30D	centrifugal granulation	Preparation and evaluation of sustained-release metformin hydrochloride pellets[37]	Result increased relative bioavailability and a sustained release effect.
7	Hydrochlorothiazide and piroxicam	HPMC and starch	Extrusion/Spheronisation	Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/Spheronisation[38]	Dissolution of both HCTZ and piroxicam was achieved: >80% drug released in 30 min.
8	Diclofenac Sodium	Carbopol 71G	Pelletization	Evaluation of diclofenac sodium release from matrix pellets compressed into MUPS tablets[39]	Drug release rates of formulations, with a range of 1 to 8 h to complete dissolution.
9	Budesonide	Eudragit NE30D, L30D55 and FS30	Extrusion-Spheronization	Development and evaluation of a novel pellet-based tablet system for potential colon delivery of budesonide[40]	drug release in stomach and small intestine of budesonide was released at 24 h.

10	Budesonide	Eudragit S100	Extrusion-Spheronization	Formulation and evaluation of sustained release enteric-coated pellets of budesonide for intestinal delivery[41]	Drug release in the stomach followed by release for 12 h in the intestinal pH.
11	Budesonide	Eudragit E100 and FS30D	Extrusion-Spheronization	Development of novel budesonide pellets based on CODES(TM) technology: In vitro/in vivo evaluation in induced colitis in rats[42]	Release rate was controlled in buffer of pH 6.8 by the type and amount of polysaccharide
12	Borneol	Eudragit L30D-55, Eudragit L100 and Eudragit S100	Bottom Spray Coating (FBP)	Preparation of the traditional Chinese medicine compound recipe heart-protecting musk pH-dependent gradient-release pellets[43]	pH-dependent gradient sustained release under the simulated gastrointestinal pH conditions
13	Norfloxacin	HPMC K15M and Eudragit RL 100	Extrusion-Spheronization	Development and Optimization of a Floating Multiparticulate Drug Delivery System for Norfloxacin[44]	polymer coat increases the drug release decreases, producing sustained release up to 8hr.
14	Diclofenac	Eudragit RS100 and Eudragit L100	Extrusion-Spheronization	Biopharmaceutical Process of Diclofenac Multi-particulate Systems for Chronotherapy of Rheumatoid Arthritis[45]	pulsatile-release pellets followed zero-order kinetics up to 18 hr.
15	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[46]	Sustain drug release from Liqui-Tablet formulation up to 24 h.
16	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[47]	optimized formulation for targeted drug delivery of budesonide to colon up to 18 hr.
17	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[48]	optimized formulation for targeted drug delivery of 5-fluorouracil to colon up to 24 hr.
18	Rifampicin and Isoniazid	Eudragit L-100	Extrusion-Spheronization	Formulation And Evaluation Of enteric of Rifampicin and Isoniazid With Improved Rifampicin Stability.[49]	Drug release for Rifampicin was found to 89 % in formulation.
19	Aceclofenac	Ethyl cellulose N50 and HPMC E5	Fluid bed processor	Design and evaluation of sustained release pellets of Aceclofenac[50]	Drug release up to 28 hrs. were found in pH 6.8 phosphate buffer from sustained release pellets.
20	Mesalamine	Eudragit RSPO,	Fluid bed	Design, Development and	optimized

		Eudragit RL PO and Eudragit L100	processor	Characterization of Extended Release Multiunit Particulate System of Anti-Inflammatory Drug[51]	formula of mesalamine multi-unit particulate system was stable and Can be release into lower part of intestine.
21	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[52]	Drug release from the sustained release pellets in pH 7.4 or 7.5 phosphate buffer up to 8 hours.
22	Disopyramide phosphate	Eudragit L 100 and S 100	Extrusion-Spheronization	Development and evaluation of porous membrane pellets of Disopyramide phosphate for sustained release[53]	The drug release was sustained up to 12 hrs.
23	Torsemide	Ethyl cellulose, Eudragit L30 D 55 and Eudragit NM 30 D	Extrusion-Spheronization	Formulation and evaluation of Torsemide pellets for extended drug release by extrusion-spheronization method[54]	The drug release was Extended up to 24 hrs.
24	Metoprolol Succinate	Ethyl cellulose, HPMC, Di ethyl phthalate	Fluid bed processor	Formulation and In vitro Evaluation of Metoprolol Succinate Extended Release Pellets.[55]	Controlled drug release observed and can reduce the dosing up to once daily.
25	Azithromycin	Ethyl cellulose and HPMC	Extrusion-Spheronization	Using Extrusion–Spheronization to Develop Controlled-Release Formulations of Azithromycin[56]	Controlled drug release observed and drug release data fitted to a first-order release kinetics model.
26	Diltiazem Hydrochloride	Ethyl cellulose	Extrusion-Spheronization	Use of Extrusion–Spheronization to Develop Controlled-Release Dosage Forms for Diltiazem Hydrochloride[57]	The drug release followed first-order kinetics and desired drug released in controlled manner.
27	Theophylline	glyceryl monostearate	Extrusion-Spheronization	Development and In Vitro Evaluation of a Novel Multiparticulate Matrix Controlled-Release Formulation of Theophylline[58]	Controlled drug release observed and drug release data fitted to a first-order release kinetics model.
28	Verapamil Hydrochloride	Ethyl cellulose, Eudragit NE30D and Eudragit-RS100	Extrusion-Spheronization	Design and development of Multiple-Unit, Extended release drug delivery system of Verapamil HCL by Pelletization Technique[59]	Extended drug release from formulation was achieved up to 24 hrs.
29	5-fluorouracil	Ethyl cellulose	Extrusion-Spheronization	Colon-specific delivery of 5-fluorouracil from zinc pectinate pellets through in	Drug was released upon prolonged

				Situ intra-capsular ethyl cellulose–pectin plugs formation[60]	dissolution and in response to colonic enzyme pectinase
30	Esomeprazole and Naproxen	Eudragit RS30D, RL30D and Eudragit L30 D55	Fluid bed processor	Novel naproxen/esomeprazole magnesium compound pellets based on acid-independent mechanism: in vitro and in vivo evaluation[61]	Sustained in vitro drug release was found. NAP-CSPs had effective dissolution and absorption in the colon.
31	Capecitabine	Eudragit S100/Eudragit-L100 and Surelease	Extrusion-Spheronization	Multiple response optimization of processing and formulation parameters of pH sensitive sustained release pellets of capecitabine for targeting colon[62]	Optimized Eudragit/Surelease coated capecitabine pellets showed sustained drug release in the colon tissue up to 23 hrs.
32	Nateglinide	Kollidon® SR (K-SR)	Extrusion-Spheronization	Formulation and IN-vitro characterization OF sustained release matrix pellets OF nateglinide.[63]	Nateglinide sustained release matrix pellets showed 100% drug release up to 12 hrs.
33	Metformin	Ethyl cellulose and Eudragit RS 100	Fluid bed processor	Preparation of Sustained Release Metformin Tablet from Reservoir Pellets[64]	Metformin sustained release showed 100% drug release within 12 hrs.
34	Cefixime	Eudragit RS100 and Eudragit RL100	Extrusion-Spheronization	Design and Development of Fast Disintegrating Tablet to form Sustained Release Suspension of Cefixime by Extrusion and Spheronization Technique[65]	Drug release from sustained release suspension up to 12hrs.
35	Tizanidine hydrochloride	Ethyl cellulose N-50, Eudragit L-100	Fluid bed processor	Design and Evaluation Of Sustained Release Multiparticulate System Of Tizanidine Hydrochloride[66]	Optimized formulation followed zero order kinetics by non-Fickian case-II diffusion process
36	Ambroxol	Ethyl Cellulose N50	Fluid bed processor	Modified release capsules of Ambroxol, Preformulation and evaluation[67]	Modified release pellets in capsule have more drug release rate.
37	Rabeprazole sodium	Eudragit L30 D55	Fluid bed processor	Formulation and evaluation of delayed release pellets of Rabeprazole Sodium.[68]	Optimized formulation showed delayed release of drug up to in pH 6.8.
38	Tamsulosin HCl	Eudragit L-100, Ethyl cellulose N-50	Fluid bed processor	Formulation Development and In-vitro Evaluation of Tamsulosin HCl Extended	Optimized pellets formulation extended drug

				Release Pellets.[69]	release with similarity factor 73.45
39	Indomethacin	Hydroxy propyl methyl cellose, Ethyl cellose	Fluid bed processor	Design and evaluation of multi particulate system of extended release indomethacin capsules USP[70]	Drug release from optimized extended release formulation showed up to 12hrs.
40	Itopride hydrochloride	Ethyl cellulose, Eudragit RL/RS 100, and Kollicoat® SR 30D	Extrusion-Spheronization	Formulation development and characterization of highly water-soluble drug-loaded extended-release pellets prepared by extrusion–spheronization technique[71]	Extended-release pellet formulation of ITP can be a good oral alternative formulation for the treatment of gastrointestinal disorders
41	Ambroxol Hydrochloride	Eudragit RL 30 D and Eudragit RS 30 D	Extrusion-Spheronization	In vitro Release Kinetics Study of Ambroxol Hydrochloride Pellets Developed by Extrusion Spheronization Technique Followed by Acrylic Polymer Coating[72]	Optimized formulation showed sustained release of drug up to 12 hrs. in pH 6.8
42	Indomethacin	Hydroxypropyl methylcellulose E5 LV premium	Extrusion-Spheronization	Indomethacin sustained release pellets prepared by extrusion-spheronization[73]	Formulation of sustained release pellets successfully controlled the drug release
43	Losartan potassium	Eudragit RS and PEG 6000	Extrusion-Spheronization	Losartan potassium sustained release pellets with improved in vitro and in vivo performance[74]	Sustained release matrix pellets successfully controlled the drug Release up to 8hrs.
44	Flurbiprofen	Carbopol 934, HPMC K10	Extrusion-Spheronization	Optimized flurbiprofen sustained-release matrix pellets prepared by extrusion/spheronization[75]	Sustained-release pellet formulation of FBP was able to sustain the release of Flurbiprofen for up to 8 h.
45	Famotidine	Pluronic F-127 and Gelucire 50/13	Solid dispersion	Formulation of immediate release pellets containing famotidine solid dispersions[76]	drug release of formulated pellets by solid dispersion was found extend up to 2 hrs.
46	Meclizine HCl	Glyceryl monostearate, Glyceryl palmitostearate, Glyceryl behenate	Extrusion-Spheronization	Lipids bearing extruded-spheronized pellets for extended release of poorly soluble antiemetic agent meclizine HCl[77]	Encapsulated pellets of Meclizine HCl can be effectively used for treatment

		and Carnauba wax			of motion sickness, nausea and vertigo for extended period of time.
47	Tamsulosin hydrochloride	Eudragit NE30D and Eudragit L30D55	Fluid bed processor	Preparation and evaluation of tamsulosin hydrochloride sustained-release pellets modified by two-layered membrane techniques[78]	Sustained release pellets successfully drug Release up to 6hrs in pH 7.2 media.
48	Diltiazem hydrochloride	Ethyl cellulose & Hydroxyl propyl methylcellulose phthalate	Fluid bed processor	Development and evaluation of diltiazem hydrochloride controlled-release pellets by fluid bed coating process[79]	Fluid bed coating process showed controlled release of diltiazem HCl for a prolonged period of time i.e. up to 16 hrs.
49	Budesonide	Eudragit S100	Fluid bed processor	Formulation and evaluation of sustained release enteric-coated pellets of budesonide for intestinal delivery[80]	Optimized formulation showed negligible drug release in the stomach followed by release for 12 h in the intestinal pH.
50	Clozapin	Hydroxyl propyl cellulose and glyceryl palmito stearate	Extrusion-Spheronization	Development and evaluation of clozapin pellets for controlled release.[81]	Controlled release pellets successfully drug Release up to 24 hrs in intestine.

Pharmaceutical patents for pellets dosage forms:

Several pharmaceutical organizations have patented various pellets dosage forms for the controlled release of drugs. These patents often involve unique formulations and technologies aimed at improving drug delivery systems. Some notable patented pellet formulations described below in table 4 include those for sustained-release formulations, multiparticulate systems, and gastro-resistant pellets, among others.

Table 4: Various patents for pharmaceutical pellets products along with applications

S.no.	Patent	Title	Drug	Application of drug
1	US5958458	Pharmaceutical multiple unit Particulate formulation in the Form of coated cores[82]	Theophylline	Treatment of asthma
2.	WO2004091583	Time-Controlled Release Formulations And Atrial Fibrillation Treatment Method[83]	Diltiazem	Antihypertensive
3	WO2004050064	Process For Manufacturing A Controlled Release Formulation By Means Of A Pastiler[84]	Benzimidazole derivatives	Anti-cancers, Antivirals, Anti-hypertensive, Antifungals And Anti-Diabetics
4	US2004048814	Sustained release composition containing clarithromycin[85]	Clarithromycin	Antibacterial
5	US6984402	Chrono delivery formulations	Methylphenidate	Attention deficit

		and method of treating atrial fibrillation[86]		hyperactivity disorder
6	WO2007011131	Stable controlled-release pellet containing tolterodine[87]	Tolterodine	Antimuscarinics
7	WO2007138022	Lipoic Acid Granules[88]	Lipoic acid	Treating diabetic nerve pain, healing wounds, lowering blood sugar.
8	WO2007073894	Oral preparation with controlled release[89]	Metoprolol	Antihypertensive
9	WO2008064734	Medicament with controlled release Galanthamine[90]	Galanthamine	Treatment in Alzheimer's disease
10	WO2009042778	Controlled release pharmaceutical composition[91]	Carbamazepine/ Mesalamine/ Propafenon	Anticonvulsant/ treat ulcerative colitis/ Treat arrhythmia
11	WO2001015668	Controlled release pellets formulations[92]	Verapamil	Antihypertensive
12	WO2002028376	Chrono Delivery Formulations And Method Of Use Thereof[93]	Diltiazem	Antihypertensive
13	WO2004002398	Spherical pellet containing a water-soluble active ingredient[94]	Tramadol	Analgesics
14	WO2007117110	Sustained-release pellets containing tamsulosin hydrochloride and processes for preparing the same[95]	Tamsulosin	Treatment in benign prostatic hyperplasia
15	US20090297597	Modified Release Ticlopidine Compositions[96]	Ticlopidine	Reduce the risk of thrombotic strokes
16	US20100136106	Modified Release Famciclovir Compositions[97]	Famciclovir	Treat herpesvirus infections
17	WO2004058257	Controlled release formulation comprising benzimidazole derivatives or pharmaceutically acceptable salts thereof with increased stability and method for preparing the same[98]	Benzimidazoles	Anti-cancers, Antivirals, Anti-hypertensive, Antifungals And Anti-Diabetics
18	WO2007017253	Oral preparation with controlled release of a benzenesulphonamide[99]	Benzenesulfonamides	Treatment of proliferative diseases (cancer)
19	WO2008102192	Controlled release pharmaceutical compositions[100]	Carvedilol	Antihypertensive
20	WO2009002416	Controlled release tamsulosin hydrochloride formulation[101]	Tamsulosin	Treatment in benign prostatic hyperplasia
21	WO 2014124700 A1	Multiparticulate pharmaceutical composition comprising a multitude of two kinds of pellets[102]	Metoprolol	Antihypertensive
22	WO 2013122554 A1	Pellet formulations comprising esomeprazole[103]	Esomeprazole	Treat heartburn, acid reflux and gastro-oesophageal reflux disease
23	WO 2009002416A1	Controlled release Tamsulosin Hydrochloride Formulation [104]	Tamsulosin	Treatment in benign prostatic hyperplasia

CONCLUSION

Miracle in pellets dosage forms refers to the advantages of using pellet-based drug delivery systems, such as improved drug stability, controlled release, and enhanced patient compliance. The conclusion typically emphasizes the promising potential of these forms in offering targeted and sustained drug delivery, thus enhancing therapeutic outcomes and minimizing side effects. Additionally, it highlights the need for further research and development to harness the full benefits of this technology in pharmaceutical applications. The future prospects of pellets dosage forms are promising, with continued advancements expected in the field of pharmaceutical technology. This includes the development of novel pellet formulations for personalized medicine, targeted drug delivery, and improved bioavailability. Moreover, the integration of nanotechnology and biodegradable polymers is anticipated to revolutionize the design of pellets, enabling precise control over drug release kinetics and enhancing therapeutic efficacy. Furthermore, the potential for incorporating multifunctional coatings and stimuli-responsive materials may further expand the scope of pellets in delivering drugs with enhanced precision and efficiency.

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