



## Review article

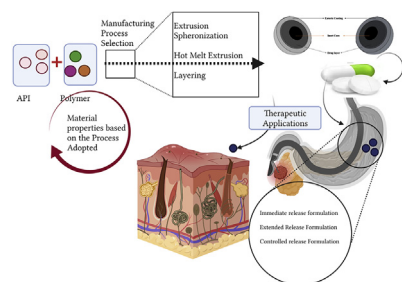
## Quality aspects in the development of pelletized dosage forms

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## GRAPHICAL ABSTRACT



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## ABSTRACT

The aim of this work was to identify and collate the major common challenges that arise during pellet development. These challenges focus on aspects right from raw material properties until the final drying process of the pelletization. The challenges associated with the particle size of drug and excipients, physicochemical properties, drug excipient interaction and the effect of type/grade and amount of raw material on the pellet properties are covered in this review. Technological and process related challenges within the commonly used pelletization techniques such as extrusion-spheronization, hot-melt extrusion and layering techniques are also emphasized. The paper likewise gives an insight to the possible ways of addressing the quality of pellets during development.

## 1. Introduction

The pelletized drug delivery is gaining paramount importance in therapeutics owing to their narrow range of particle size, good flow properties, and less friability, which prevents dose dumping. The technological advancement has added a new horizon in the manufacturing and scalability of these drug deliveries [1]. There have been many investigations on optimization of these formulations controlling process parameters and polymers added to obtain pellets of high quality [2, 3]. The schematic representation in Figure 1 gives a review of drug delivery development and applications, which are critical in terms of polymer and manufacturing method selection. The various pelletization techniques are extrusion-spheronization, Hot-melt extrusion, Layering techniques,

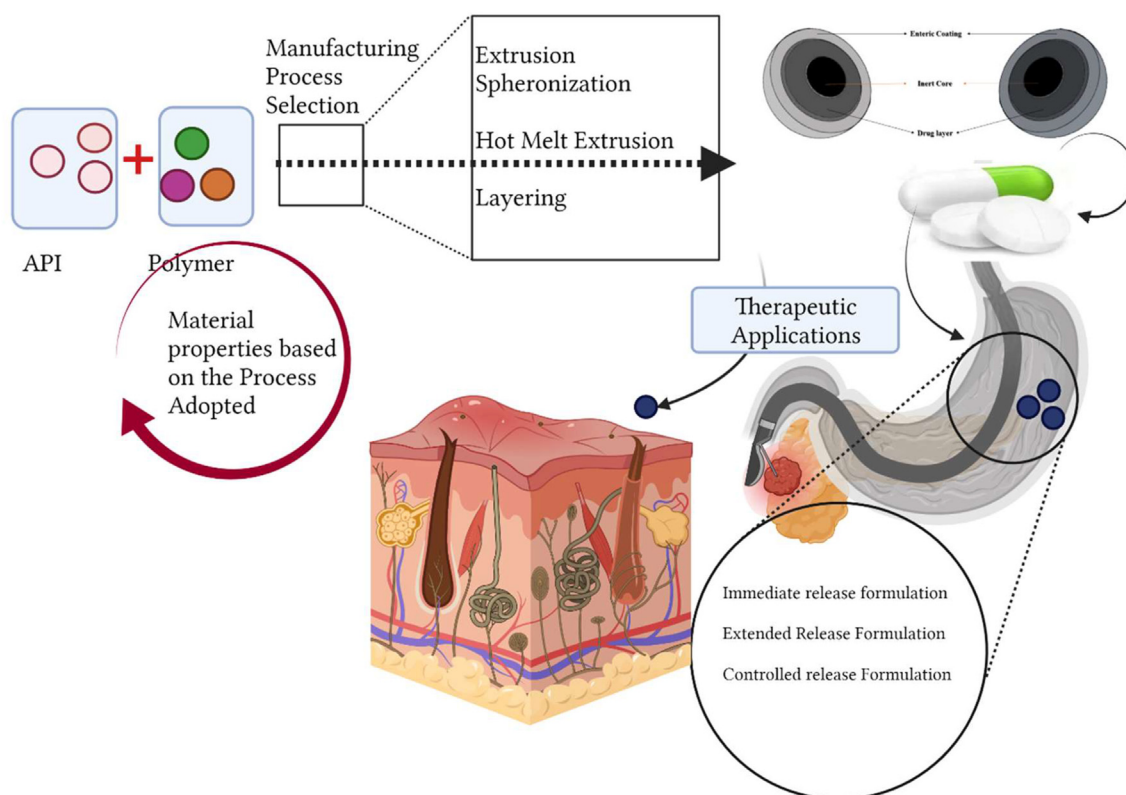
Balling (Spherical agglomeration), Compression, Globulation, Spray drying, Spray congealing and cryopelletization are used [4, 5, 6].

Each technique listed above is superior based on the application for which pelletized drug delivery being manufactured. Therefore, determining critical process parameters that influence the quality of the product is important during development process [7, 8, 9]. A deep understanding of these process parameters and material property help in reducing the batch manufacturing deviations leading to a robust product [10, 11, 12].

The studies in the past highlights the different approaches to pelletization, but there has not been a study collating the possible challenges that come in the way. In this review, major challenges that arise within the formulation, process and technological aspects during pellet

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**Figure 1.** Important aspects during Pelletized drug delivery development.

development are discussed. The report explains the effect of various types, grades and quantity of drug and excipients on the pellet properties [13, 14, 15, 16]. It also discusses the challenges that could occur due to change in processing parameters like time, temperature, speed of the equipment used in pelletization [3, 15, 17, 18].

## 2. Impact of material attributes

An initial inspection and evaluation of physicochemical properties of the raw material is very essential. By virtue of their inherent properties, the drug-excipients may be either in the completely dissolved or undissolved state in the final dosage form [13, 19]. This state of the drug in dosage form could be the result of processing which have an immense impact on the stability of the product.

### 2.1. Impact of particle size and shape on process and product

The particle size of the starting material such as drugs, polymers and binders impacts the surface roughness of the pellets [18]. Small particles pack well and leaves less peaks and valleys. Hence, the smaller the particles size the smoother is the surface of the pellets [20, 21]. Starting materials, such as Microcrystalline cellulose (MCC) gives pellets with smoother surfaces than those produced by crosspovidone or lactose. This

is because MCC disaggregate into smaller particles during the wetting process [22]. Therefore, the surface roughness of the pellet depends upon the particle size of the disaggregated particles. In addition to MCC, further smoothness of the pellets could be attributed to formation of gel following pellet shrinkage [23].

### 2.2. Impact of API property on processing

The critical material attributes significantly affect the choice of pelletization process as listed in Table 1. Powder containing high concentrations of hydrophobic drugs are difficult to extrudate and spheronize due to poor wettability of the powder mass. Hydrophobic drugs impart good tensile strength to the pellets due to its low water concentration and it also slows the dissolution time [29]. On the other hand, Hydrophilic drugs show uniform wettability of the powder mass. They tend to agglomerate because of their high-water concentration. Pellets produced with hydrophilic drugs are of low tensile strength and shows faster dissolution rate. Pellets of drugs of low solubility show narrow distribution of size when compared to pellets of high solubility drugs [30, 31].

The hot melt extrusion converts the extruded rods to compactable material and thereby overcomes all compressibility problems during tableting [32]. The research proved that the materials melt under the

**Table 1.** Impact of critical material attributes on critical quality attributes of Pelleting Process.

Critical material Attributes	Critical Quality Attributes	Processing changes	References
Particle Size	Blend Uniformity	Change in the type of mixer and optimization of blending	[11]
Particle Size distribution	Blend uniformity and pellet size	Particle sizing and optimization of blending	[24]
Fines/Oversize	Content uniformity	Order of addition, Number of revolutions (Speed & Time)	[25]
Particle shape	Sphericity of the pellets	Spheronization Speed & Time)	[24, 26]
Compaction behaviour	Friability and Hardness of the pellets	Addition of type of binder and concentration	[27]
Moisture content	Material loss during processing, friability and hardness of the pellets	Environmental temperature and relative humidity	[28]

processing conditions and affect the functionality of other ingredients [33]. It has been reported inhibition of hardening of Polyethylene glycol (PEG) PEG-MCC matrix by fenoprofen calcium, resulting in an impracticable product [34]. In another work Lidocaine lowered the T<sub>g</sub> of Eudragit E/high-density polyethylene (HDPE) films [35], and a time-dependent lowering of the glass transition temperature of hydroxypropyl cellulose (HPC) films was observed with hydrocortisone [36].

### 2.3. Water content during processing

Water content is the most important factor that influences the pellet size, pellet size range and the pellet shape. The pellet size increases with an increase in the water content. The water content is dependent on the type of drug. At high water concentration, pellets of powder masses especially with hydrophilic drugs agglomerate during spheronization [37, 38] While wet-massing, water at a low concentration does not impart sufficient plastic properties and hence the pellets prepared by such a less wetted mass are not spherical. The bulk and tapped densities as well as the flow rate increases with an increase in the concentration of water [39]. Therefore, it is necessary to use an optimum concentration of water to get pellets of desired size, sphericity and smaller size range. A research demonstrated that the addition of Glyceryl monostearate (GMS) to the powder mass could be beneficial for drug that are moisture sensitive or sensitive to the heat energy required to evaporate the water, as GMS decreases the water concentration in the formulation. GMS also imparted smoother surface and less porosity to most formulations. However, during extrusion and spheronization process, the length of the extrudates and thereby the pellet size increases when GMS concentration is increased [40, 41]. Basically melt extrusion process avoids latent drug degradation due to hydrolysis and thereby proved to be effective and most preferred anhydrous process for hydrolyzable drugs [10, 42].

### 2.4. Impact of binders on processibility during extrusion spheronization

Both the binder concentration and the type of binder affect the physical properties and appearance of the pellets. During the spheronization process, pellets of larger size and less sphericity are obtained as the binder concentration is increased. Because with a high binder concentration, the small particles combine with one another or with the large particles to form even larger particles [14, 43, 44, 45].

Compared to other binders such as Methocel E15 LV, Methocel A4M, HPC-L, certain binders such as HPC-M show less effects on pellet size and sphericity at higher concentrations. More spherical pellets, a narrow size distribution and good flow could be obtained by increasing the HPC-M concentration [46, 47, 48].

### 2.5. Impact of commonly used polymer properties during extrusion spheronization

Thermoplastic behaviour of the polymer and formulation plays a crucial role while selecting a polymer. The important factor is the compatibility and stability of the plasticizer-polymer mixture. Most commonly used plasticizers are Triacetin [49], citrate esters [50], and low molecular weight polyethylene glycols [51]. The type and level of plasticizer determines the extent of glass transition (T<sub>g</sub>) lowering for a particular polymer which thereby improves the stability of API and polymer [52, 53]. The high molecular polymers can be processed very easily by lowering shear forces. The lowering of those shear forces helps them extrude out of the extruder [54, 55]. Other parameters in the selection of plasticizer are thermostability and volatility of the plasticizer [56].

#### 2.5.1. Microcrystalline cellulose (MCC)

Due to its excellent plastic behaviour and cohesiveness when wetted and its capacity to uptake, hold and yield water; MCC parts acceptable shape, size, mechanical resistance and flow properties to pellets. Hence,

it is the most preferred aid for pellet formulation [18, 57]. Different grades of MCC show significant difference in their physical properties, which influences the water uptake. Even though MCC grades that possess high bulk density, lower porosity and good water retentive capacity produce equivalent size pellets, these pellets are less spherical and are observed to show more shape variations [58, 59]. MCC exhibits batch variability as it is derived from natural sources. Moreover, research proves that MCC has been chemically incompatible with some drugs [2, 60]. Another limitation is that MCC increases the dissolution time of pellets due to its high cohesive strength [61, 62]. Therefore, MCC may be replaced with alternative excipients such as crosspovidone, carrageenan, pectinic acid, cellulose derivatives (Hydroxypropylmethyl cellulose, hydroxyethyl cellulose), polyethylene oxide, modified starches, glycerides, chitosan,  $\beta$ -cyclodextrin and sodium alginate [22, 63]. Challenges faced with some of the widely used pelletization aids are discussed below.

#### 2.5.2. Cross Polyvinylpyrrolidone (Crosspovidone)

Crosspovidone is a cross-linked synthetic polymer, which possesses a water reservoir. Like MCC, the rigid and flexible cross-linked structure facilitates absorption, release and reabsorption of water during wetting, extrusion and spheronization respectively. However, Crosspovidone requires more amount of water as compared to MCC [17]. Although it produces pellets of larger size, the particle size range of pellets is narrow. The use of crosspovidone with negligible water added, removes the necessity of binder addition. Crosspovidone imparts shorter dissolution time as compared to MCC due to its superior disintegration property [64, 65].

#### 2.5.3. Carrageenan

Carrageenans are acid polysaccharides isolated from the cell walls of the red seaweeds. It is capable to replace MCC due to its ability to produce pellets of adequate quality and fast drug release. Carrageenans immobilize more water, imparts good size distribution and results in very fast drug release. However, carrageenans make the pellets highly porous and hence yield pellets of lower tensile strength as compared to MCC [22, 23].

#### 2.5.4. Pectin

Pectin is a gel-forming, non-toxic polysaccharide ideal for colon-targeted drug delivery. The quality of pectin based pellets depends on the concentration and type of additive used in the granulating liquid. The mucoadhesive pellets prepared shows superlative property. Research demonstrates that amidated pectin produced short and nearly spherical pellets with the use of ethanol in the granulating liquid. However, these pellets lack mechanical strength and are likely to disintegrate faster thereby imparting a high dissolution rate in acidic as well as basic buffer to the pellets [66, 67, 68, 69, 70].

## 3. Processing challenges

The most commonly investigated pelletization techniques are Extrusion-Spheronization and suspension/solution/powder layering techniques. Hot melt extrusion is another pelletization technique of increasing importance. The challenges associated with these techniques are discussed below.

### 3.1. Process related challenges in extrusion – spheronization technique

Extrusion-Spheronization is the most widely used pelletization technique due to its cost-effectiveness and its ability to produce high quality pellets. It is a three-step process: 1. Wet Massing, 2. Extrusion and 3. Spheronization [71]. There are several critical parameters for these three stages and has great influence on pellet characteristics. These parameters include type and concentration of drug and other excipients (as discussed

earlier), Extruder type, extrusion pressure and speed and spheronization speed, pressure and time [16, 72].

K.Thoma investigated the effect of different types of extruders on extrusion behaviour and sphere characteristics [73]. It was observed that the extrudates from three different types of extruders possessed certain difference in their properties. These differences in the extrudates further impacted the pellet size and other physical properties of the pellets. It has been demonstrated that the spheronization speed and time impacted the size of the produced pellets [74]. An increase in the speed of the Spheronizer resulted in a decrease in the pellet size. The smaller pellets also showed a difference in the dissolution profile [75].

Agrawal et al reported that the pellet shape is highly affected by the spheronization time. The pellets become more round as the spheronization time is increased till an optimum level, after which very little difference is seen in the roundness [76]. In addition to the spheronization time, the pellets shapes were also affected by the rotational speed of the friction plate [77]. However, the attribution force imparted by increase in spheronization time at lower speed is greater than that at decreased spheronization time and increased speed, thus producing more circular pellets and rendering the pellets more flowable [78].

### 3.2. Process related challenges in hot melt extrusion technique

Hot met extrusion has certain advantages over conventional pelleting techniques such as shorter processing time, eliminates the use of solvents and enhances drug delivery. However, it is a challenging process due some limitations. These include degradation of thermolabile drugs, requirement of raw materials possessing high flow properties, limited options for heat stable polymers and high energy requirement. These limitations increase the overall costs of production [79].

The most preferable processing can be done at temperature above the M.P. of semi-crystalline polymers or [50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100] °C above the glass transition temperature Tg of amorphous polymers, but below the M. P. of the crystalline API [80, 81].

According to Breitreutz et al., the material temperature control is the most critical factor on the spheronization of solid lipid based extrudates, which can be corrected by reducing the wall jacket temperature and employing an external source of heat: an IR light. This changed exposure area of the material to the heat source making it very small in comparison with the commonly used conventional setup [82].

### 3.3. Process related challenges in layering techniques

Solution/suspension layering and dry powder layering techniques are used to prepare high drug potency and controlled release pellets. These techniques often pose challenges such as increase in pellet size, rough pellet surface due to larger particle size of the coating materials and blockage of the nozzle resulting in non-uniform layering [83, 84]. The surface of the pellets becomes porous due to inappropriate type or concentration of binder. An increase in binder concentration will increase the surface smoothness of the pellet but it decreases the potency. Other parameters that affect the pellet characteristics are weight of the core pellet, solution/suspension/powder application rate, atomizer's type, position and speed, temperature, atomization degree and air cap [85].

### 3.4. Challenges related to drying process

Research has illustrated that the drying process has a significant impact on the mechanical strength, surface properties and the drug release profile of formulated pellets [86] Although Pellets dried on a tray dryer possess more diametrical strength and greater crushing strength, these pellets show less elasticity. The lengthy drying time used on tray dryer enhances the in-vitro drug release of tray-dried pellets. However, lengthy drying time hampers the surface smoothness of the pellets and

may even degrade certain drugs [86, 87]. On the other hand, the drying time for drying pellets on a fluidized bed dryer is shorter as compared to the tray drying, thus eliminating the risk of thermal degradation of drug. Pellets dried over a fluidized bed dryer are more elastic and possess a smoother surface as compared to pellets dried over a tray dryer. However, these pellets possess less mechanical strength and exhibit slow dissolution rates [88]. The drying temperature also affects the pellet size. Scientist proposed that the pellets begin to shrink with an increase in temperature resulting in smaller particle size [75].

## 4. Release modifications for different applications

### 4.1. Improve solubility and dissolution of poorly water soluble drug

A 30 fold increase in the dissolution rate of 17-Estradiol hemihydrate (10 % w/w) compared to pure drug has been reported by using PEG 6000, polyvinylpyrrolidone or a vinylpyrrolidone vinyl acetate-copolymer along with Sucroester® WE 15 or Gelucire® 44/14 as additives [89].

The increase in solubility of carbamazepine was reported by using d-gluconolactone (GNL) in hot melt extrusion [90]. The solid dispersion prepared with Eudragit EPO by hot-melt extrusion (HME) in the drug: carrier ratio of 4:1 resulted in more than 85 % drug release in just 5 min [91]. Hot melt extrudes of carbamazepine were compared against simple physical mixture for improvement in solubility and dissolution by using polyethylene glycol 4000 (PEG 4000) as a hydrophilic carrier and low melting binder. The extrudates obtained with uniform shape and density revealed much faster release as compared to the physical mixture [92, 93].

The solid dispersion of curcumin using different ratio of Poloxamer 407 by melt method were finally extruded and spheronize. The resulting pellets showed increase in solubilisation however it is noteworthy that pelletization process had no impact on solubilisation of solid dispersion [94], were formulated as pellets without any impact on drug release profile.

### 4.2. Sustained/controlled release/enteric release dosage form

Matrix type enteric or sustained release pellets can be produced by extrusion spheronization or hot melt extrusion whereas the reservoir type contains drug core embedded by polymer layer [95, 96].

Nakamichi and co-workers developed the sustained release pellets of nifedipine hydrochloride and hydroxypropyl methylcellulose acetate succinate using twin-screw extruder. The position of screw element and the barrel temperature were considered as a critical factor in obtaining a puffed mass which thereby exhibits a floating property by lowering density. The pellets were retained for long period in the stomach as discrete floating particles releasing drug for 24 h [97].

The sustained release gastro-retentive floating pellets of Diltiazem hydrochloride filled into capsule were made using ethyl cellulose, cellulose acetate butyrate (CAB), poly (ethylene-co-vinyl acetate) (EVAC) and polymethacrylate derivative (Eudragit® RSPM) by Follonier et al. The parameters which affected the release of diltiazem hydrochloride were polymer type, drug/polymer ratio, and pellet size. The release rate was optimized by incorporating croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (Explotab) into the formulations. The pellets produced, exhibited a smooth surface and low porosity by the use of triacetin and diethyl phthalate as plasticizers [98]. The sustained release tablet were also explored from the pellets prepared using cheaper excipients and exhibited marginal difference in the performance [99].

Kleinebudde & Reitz, 2009 developed sustained release matrix spheres by solvent-free spheronization process. A binary lipid mixture with different amounts of Witocan 42/44®, Dynasan 114® and theophylline as model drug were used to produce extrudates. The proper control on jacket temperature and maintaining low product temperature helped

in achieving spherical sustained release matrix pellets with low porosity, defined surface area and narrow particle size distribution [100].

Various wax polymers have been accessed to produce a controlled release dosage form by hot melt extrusion. Diclofenac as a model drug and carnauba wax were processed and it was found that a wax matrix with high mechanical strength could be obtained even at temperatures below the melting point of the wax. The dissolution release was strongly influenced by the formulation of the granules with different concentrations of hydroxypropyl cellulose, methacrylic acid copolymer (Eudragit L-100) and sodium chloride [101]. Some of the most attractive investigations by researchers in preparation of controlled release dosage form are low processing temperatures, high kneading and dispersing ability, and low residence time of the material in an extruder [102]. Melt extrusion technology has helped the researchers in the development of controlled release reservoir systems consisting of polyethylene vinyl acetate (EVA) copolymers and thereby lead to Implanon<sup>®</sup> and Nuvaring<sup>®</sup> technology successfully [53, 103].

A controlled release of 24 h achieved by using SLS as pore forming material in blend of Glyceryl Palmito-Stearate, microcrystalline cellulose, Sodium Alginate along and olanzapine (20: 55: 05: 20 % w/w) [103, 104]. The study suggests that a small concentration of surfactants in a mixture of lipid and MCC successfully controls the release rate from delivery devices.

The enteric coated pellets of Ketorolac were prepared by incorporating Eudragit/microcrystalline cellulose (Avicel PH 101) using extrusion/spheronization technique. Release was less than 10 % in acidic medium whereas it was complete within 60–120 min in phosphate buffer (pH 6.8) for optimized formulation [105].

The nanocrystalline ketoprofen was converted into pellets to modify the release from drug delivery. As the corn starch was utilized for making pellet, the release rate of ketoprofen increased however the drug recovery was problematic. Therefore, Cremophor<sup>®</sup> RH 40 was added during pelletization process resulting in sustained release [106].

Nandgude et al formulated the modified release pellets of Apremilast using microcrystalline cellulose (MCC), lactose, TKP, and crosspovidone. Addition of 10% Eudragit L100 was able to sustain the release up to 5 h [107].

The chrono-pharmacological needs were sufficed by modifying the release of Montelukast sodium pellets using ethyl cellulose coating in Wurster coater [108].

Spherical and extended-release pellets were prepared for Aspirin using four types of lipids (adepts solidus, Compritol<sup>®</sup> 888 ATO, Precirol<sup>®</sup> ATO5 and Compritol<sup>®</sup> HD5 ATO) and their admixture in different ratios by solvent-free extrusion/spheronization. The pellets met the release requirement as per USP [109].

#### 4.3. Rapidly dissolving pellets

Famotidine (FM) has low and variable bioavailability and water solubility therefore a solid dispersion using two hydrophilic carriers, namely Gelucire 50/13 and Pluronic F-127 were employed to prepare rapidly releasing pellets by extrusion/spheronization. The drug release from pellets was improved compared to tablets. Tablets containing solid dispersed pellets showed total drug released in 30 min while only 30 % release was seen in normal formulation of FM after 2 h [110].

Indomethacin, nifedipine, furosemide, ibuprofen, prednisolone and hydrochlorothiazide were extruded with a new co-processed excipient composed of microcrystalline cellulose (MCC), sorbitol, chitosan and Eudragit<sup>®</sup> E. The extrusion spheronization increased the stability and solubility of the formulation [111].

#### 5. Conclusion

From the above review, it is evident that the major challenge that occurs during pellet development is to choose the appropriate type and quantity of excipient for preparing pellets of the desired drug. Water

content drastically affect pellet properties. Similarly, change in the grade; type and/or quantity of the excipient also affect pellet properties. Different challenges are associated within different pelletization techniques and instruments. Every technique and instrument has its own pros and cons, which must be identified to choose the optimum technique and instrument for obtaining desired pellets. These challenges can further be addressed by finding the critical process parameters using Quality by Experimental Design approach.

#### 6. Expert opinion

Understanding the quality prospects of drug delivery solves the main problem of the development program. The polymer's innovations offer multiple drug release profiles, but the lack of extensive clinical studies could result in toxicity when applied. Research suggests that even the blend of existing polymers with these advanced polymers will compete well and have better safety. The inclusion of technological advances will certainly improve processing, but it will place a financial burden on the developers. The quality and excellence of the product could be achieved through controls of the existing processes and equipment. Implementing risk management and quality through design helps improve product performance and produce robust products in the shortest possible time.

Research on pelletized dosage forms is mainly limited to oral dosage forms. Much research is possible to achieve better drug solubility, stability and release modifications of powders that must be reconstituted prior to parenteral administration.

#### Declarations

##### Author contribution statement

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Data included in article/supplementary material/referenced in article.

##### Declaration of interests statement

The authors declare no conflict of interest.

##### Additional information

No additional information is available for this paper.

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