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HOT MELT EXTRUSION AND FREEZE PELLETIZATION: BETTER ALTERNATIVE FOR DRUGS HAVING STABILITY PROBLEM DUE TO PRESENCE OF WATER

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ABSTRACT

Pelletization methods like solution layering, suspension layering or powder layering and extrusion-spheronization process is the most frequently used method for producing spherical pellets which utilizes a granulating liquid such as water, requires drying steps which is time consuming. Many drugs exhibit stability problem due to the presence of water during processing and residual water during storage. In addition to that pellets produced by these techniques exhibit rapid drug release and require a film coating to provide controlled release properties. Hot melt extrusion and freeze pelletization technique is receiving a great deal of attention as alternative technique over other techniques which need water during processing and drying steps. This article reviews the recent finding in the preparation of pellets by these novel techniques.

INTRODUCTION: In recent years, there has been a growing interest in the field of pelletization to produce spherical pellets which can be changed into several dosages forms like tablet and capsule or can be administered as such. Pelletization involves size enlargement process and if the final agglomerates are spherical in shape in the size range of 0.5-2.0 mm, they are called pellets. Pellets have numerous therapeutic as well as technical advantages such as enhanced drug absorption due to involvement of large GI surface in absorption process, less gastric irritation by limiting localized buildup and dose dumping [1-3], good flowability due to uniform size and shape, high tensile strength, low friability, narrow particle size distribution, and uniform packing characteristics [2, 4, 5].

The pelletized products can improve the safety and efficacy of the active agent. The pellets are directly filled into capsule and can also be compressed into tablets [4, 6, 7]. The compression of pellets into tablets is much more ideal than enclosing them in a hard gelatin capsule [8-11]. In multiple-unit systems, the total drug dose is divided over many units. Failure of a few units may not be as consequential as failure of a single-unit system. Manufacturing of pellets using layering process such as solution layering, suspension layering or powder layering and extrusion-spheronization process have been used over the years. These processes have major limitation such as use of granulating liquid which causes stability problems during processing and storage. In recent years hot melt extrusion and freeze pelletization have been used to produce spherical pellets without the use of water.

Hot Melt Extrusion: In order to overcome the problems associated with the pellets produced by layering and extrusion spheronization technique, melt agglomeration and hot melt extrusion technique are in used in pharmaceutical industries. This method eliminates instability problem during processing and storage due to presence of water. Furthermore, pellets produced by these techniques do not require additional film coating since drug release is diffusion controlled. There is slight difference between these two methods. Melt agglomeration is a process by which the solid fine particles are bound together into agglomerates, by agitation, kneading, and layering, in the presence of a molten binding liquid. Dry agglomerates are obtained as the molten binding liquid solidifies by cooling.

Typical examples of melt agglomeration processes are melt pelletization and melt granulation. During the agglomeration process, a gradual change in the size and shape of the agglomerates would take place. It is usually not possible to clearly distinguish between granulation and pelletization. Thus granulation is considered a pelletization process when highly spherical agglomerates of narrow size distribution are produced. Conversely, an unsuccessful pelletization process may be classified as granulation [12].

During a melt agglomeration process, the meltable binder may be added as molten liquid, or as dry powder or flakes. In the latter, the binder may be heated by hot air or by a heating jacket above the melting point of the binder. Alternatively, the melt agglomeration process exploits an extremely high shear input, of a high-shear mixer, where the heat of friction alone raises the temperature of the binder and effects melting. Typically, the melting points of meltable binders range from 50 to 80°C. A lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates. Advantage and disadvantage of these techniques are given below:

Advantages:

- Any solvent or water is not used in this process.
- Drying steps are eliminated, processing steps are short.
- Entire procedure is simple, continuous and efficient.
- Uniform dispersion of fine particle takes place during processing.
- Good stability of the final product at varying pH and moisture condition.

Disadvantages:

- Requires high energy input.
- This technique cannot be applied for heat-sensitive materials owing to the elevated temperatures involved.
- Because melting or softening of the binder occurs during handling and processing steps so, lower-melting-point binder risks the situation.
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations in the production of pellets, immediate and sustained release tablets [13, 14]. Extrusion is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under pressure [15, 16]. Melt extrusion process consist of three basic steps: melting or plasticating a solid material, shaping the molten material and solidification of the material into the desired shape. A hot melt extrusion apparatus consists of a hopper, extruder inside a heated barrel having three different sections, and spheronizer (**Fig. 1**).

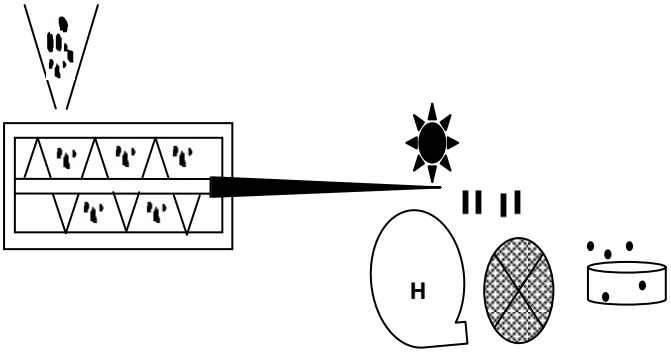


FIG. 1: SCHEMATIC REPRESENTATION OF HOT-MELT EXTRUSION

The hopper holds the material and continuously feeds into the extruder, which has a heated barrel containing the rotating screw. The extrudate is cut into uniform cylindrical segments which are spheronized into a jacketed spheronizer or supplying a heat source to spheronizer to obtain uniform size pellets. The spheronization temperature should be high enough so that it can partially soften the extrudate to facilitate its deformation and eventually spheronization.

The single screw extruder is the most important type of extruder used due to its advantages of relatively low cost, ruggedness and reliability [17]. The design of the extruder die is influenced by several variables such as composition of the extrudate as well as the operating parameters of the extruder [18]. Melt spheronization can be carried out in a single piece of equipment, such as a jacketed high shear mixer where certain components of a formulation are melted to generate spherical particles. The process is similar to wet granulation, except that the binder is in the molten state and hence does not require water or other solvent to liquefy it [19].

Materials used in Hot Melt Extrusion Technique: Most raw materials used in this technique have also been employed in conventional techniques. The material in which the drug is dispersed is called the thermal carrier or binder. During extrusion the carrier is usually transformed into a molten state. The carrier substance is usually a polymer or low melting point wax. Various meltable carriers/binders used in the formulation of sustained drug delivery systems are given in the **Table 1**. The heat due to friction generated by the screw is sufficient to melt wax. The physical and chemical properties of the carriers have significant effect on drug release characteristics. Mechanism of drug release is primarily diffusion controlled from dosage form containing water insoluble polymers and waxes such as ethyl cellulose or carnauba wax [20] and both diffusion as well as erosion from water soluble polymers such as hydroxypropyl cellulose [21, 22]. Low porosity of melt extruded dosage forms can result in incomplete drug release [23]. The incorporation of plasticizers into pharmaceutical polymer facilitates thermal processing, modify drug release properties and improve surface appearance of dosage forms.

TABLE 1: MELTABLE CARRIERS/BINDERS USED IN HOT MELT EXTRUSION

Hydrophilic Meltable Carrier/ Binder	Melting Range (°C)	Hydrophobic Meltable Carrier/ Binder	Melting Range (°C)
Gelucire 50/13	44-50	Carnauba wax	75–83
Poloxamer 188	50.9	Glyceryl stearate	54–63
Polyethylene glycol 2000	42-53	Microcrystalline wax	58–72
Polyethylene glycol 3000	48-63	Paraffin wax	47–65
Polyethylene glycol 6000	49-63	Stearic acid	46–69
Polyethylene glycol 8000	54-63	Stearic alcohol	56–60
Polyethylene glycol 10000	57-64	Beeswax	56–60
Polyethylene glycol 20000	53-66	Cetyl palmitate	47–50

Upon addition of plasticizers, thermal processing and time is reduced which diminishes the degradation of heat sensitive components [13]. Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. Wu and McGinity, 1999 reported that non-traditional plasticizers including methyl paraben and drugs such as ibuprofen were able to lower the glass transition temperature of polymeric films prepared from aqueous latex dispersion of Eudragit RS 30 D [24]. Functional excipients used in hot melt extrusion include release modifying agents which are added to improve the bulk, and processing agent which can impart specific properties to the dosage forms produced by hot melt extrusion in a manner similar to those in traditional dosage forms.

Application of Hot Melt Extrusion: In pharmaceuticals, hot melt extrusion-spheronization technique is used to disperse an active ingredient in a carrier material which must exhibit thermal stability during processing. This technique has proven to be a suitable method for the production of controlled release reservoir system and to produce sustain-release pellets. Follonier and co-workers in 1995 used this technique to produce sustained-release pellets of diltiazem hydrochloride; a relatively stable, freely soluble drug was incorporated into polymer-based pellets for sustained-release capsules [24].

Four polymers namely ethylcellulose, cellulose acetate butyrate (CAB), poly (ethylene-co-vinyl acetate) (EVAC) and polymethacrylate derivative (Eudragit® RSPM) were taken for trial. The porosity of the formulations was assessed using mercury porosimetry. The pellets produced, exhibited a smooth surface and low porosity. The in-vitro release of the drug was biphasic, with the CAB and EVAC pellets giving the lowest release rate. Similar study was

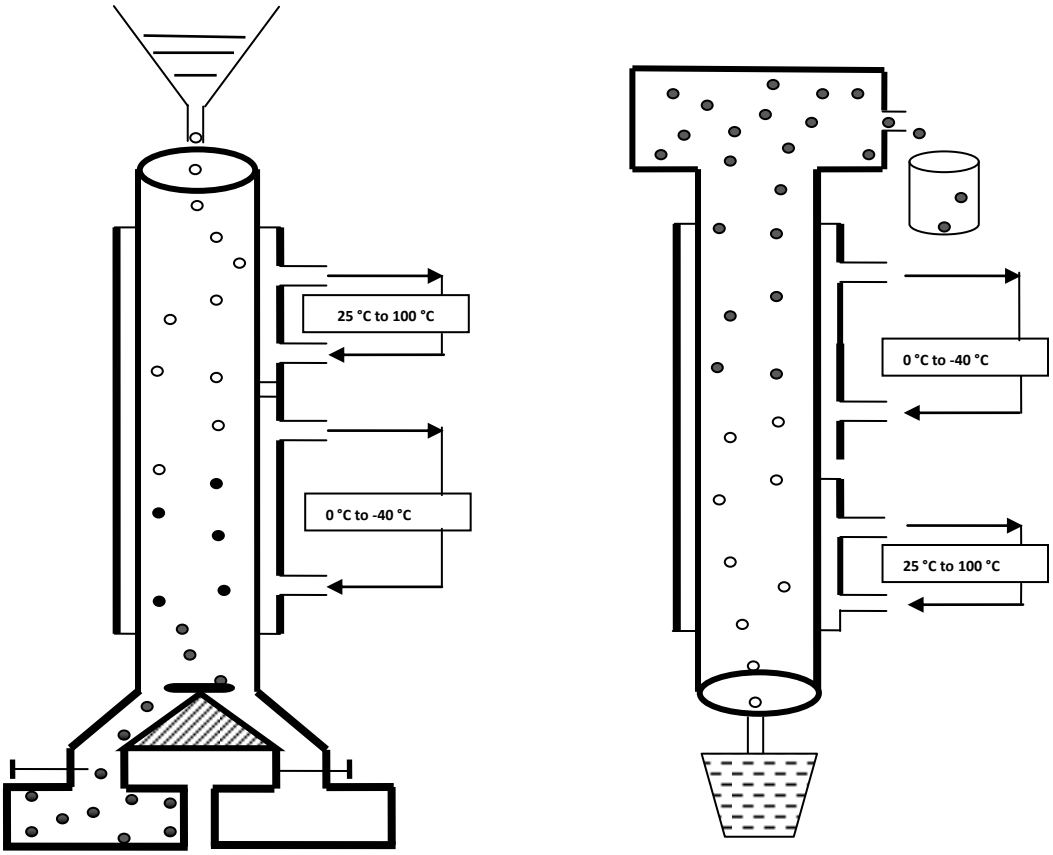
conducted by Zhang and McGinity in 2000, the objective of this study was to investigate the properties of poly vinyl acetate (PVA) as a retardant polymer and to study the drug release mechanism of theophylline from matrix tablets [14]. The release rate of the drug was shown to be dependent on the granule size, drug particle size and drug loading in the tablets. As the size of hot-melt extruded theophyllline/PVA granules was increased, there was a significant decrease in the release rate of the drug. Higher drug loading in the hot-melt granules also showed higher release rates of drug [25].

Another application of hot-melt extrusion was described by Miyagawa, Sato and coworkers in 1996, 1997 [26, 27]. They studied the controlled release mechanism of diclofenac sodium. These researchers utilized a twin-screw compounding extruder to prepare wax matrix granules composed of carnauba wax, the model drug, and other rate controlling agents. Their first investigation showed that a wax matrix with high mechanical strength could be obtained even at temperatures below the melting point of the wax. Dissolution release profiles of diclofenac from wax matrix granules were strongly influenced by the formulation of the granules. The rate controlling additives that were varied in the formulations included hydroxypropyl cellulose, methacrylic acid copolymer (Eudragit L-100), and sodium chloride.

Freeze Pelletization: A novel and simple technique of pelletization called, 'freeze pelletization' which offers several advantages over other pelletization methods, in terms of quality of pellets and process cost, producing non-porous and spherical pellets with narrow size distribution [28] and solid at room temperature so, drying is not required. Mono-disperse pellets in the size range of 1.0 mm to 5.0 mm could be prepared using this technique. In this technique, a molten-solid carrier/matrix is introduced as droplets 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. The surface/interfacial tension, density difference between pellet forming carrier solids and column liquid and the needle tip size are most important factors affecting the pellet size. The shape and wetting characteristics of the needle tips, initial column temperature and surfactant concentration in the matrix also affected pellet size. The viscosity of the column liquid was found to have a predominant effect on the shape of the pellets.

The molten-solid droplets can move upward or downward in the liquid column depending on the droplets density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is more than that of the liquid in the column, then the droplets are introduced from the top of the column and pellets solidify in the bottom portion of the column as illustrated in Apparatus I (**Fig. 2**). Conversely, if the density of the molten-solid carrier/matrix 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 the column as shown in Apparatus II (Fig. 2).

Two types of Apparatus (Fig. 2) are used and the selection depends upon the density of molten solid carrier. Suitable carriers are those which are solid at room temperature with melting point below 100°C in order to minimize degradation of active constituent. Carriers may be hydrophilic or hydrophobic in nature, melted at temperature 5-10°C higher than its melting point. The active constituent and excipients are mixed with molten carrier to form solution or dispersion.



Freeze Pelletizer I **Freeze Pelletizer II**

FIG. 2: SCHEMATIC REPRESENTATION OF FREEZE PELLETIZER I AND II

In case of Apparatus I, solution or dispersion are introduced as droplets using needles or nozzles into the inlet column of liquid and dropped from a certain height, so that droplets remain intact as they fall into the liquid column. Size of needle gauge ranges from 16-31 and its selection depends on the size of the pellets to be desired. In case of Apparatus II, the molten solid carrier is introduced from the bottom portion of the column using rubber septum. The column of both the apparatus is divided into two parts, initial portion from where molten solid carrier is introduced and is maintained between 25-100°C, and the cooling portion at which droplets solidification is maintained between 0- 40°C using cooling mixtures of acetone and dry ice. Depending on the density of droplets, the molten solid droplets move in upward or downward direction, with respect to the liquid in the column. In case of Apparatus I the molten solid carrier are introduced from upper portion of the column because density of solid carriers are more than the density of liquid used in the column and solidify in the bottom portion, while in case of Apparatus II the molten solid carrier are introduced from bottom portion of the column because density of solid carrier are low as compared to liquid used in the column and solidify at the top [29]. Following key factors should be kept in mind while using freeze-pelletization Technique:

- The molten solid carrier should be completely immiscible with the liquid in the column.
- Selection of the apparatus depends on the density of the carrier solids.
- The viscosity of the drug matrix should be low so as not to cause blockage of the needles or lead to non-homogeneity in the shape and size of the pellets.
- The particle size of active ingredient and excipients that are added to the carriers should be small enough to pass through the needles.
- The liquid in the column should have a low freezing point, preferably below -10°C.
- The optimum viscosity of the liquid should range between 4 and 40 cP at 20°C to obtain spherical pellets. If the viscosity is much lower, molten solid droplets move rapidly in the column and lose their spherical shape. If the viscosity is greater, then the pellets move too slowly and they may form agglomerates.
- The rate at which droplets are introduced into the column should be optimized to prevent aggregation of the pellets.

Materials used in Freeze Pelletization Technique: Molten-solid matrices in this technique are composed of molten-solid carriers, in which actives and excipients are dispersed or dissolved. Excipients in the matrix can be diluents, disintegrating agents, surfactants, or release-modifying agents. Various hydrophilic and hydrophobic solids are suitable as carriers. Suitable carriers are solid at room temperature and melt below 100^{o}C to minimize the degradation of the actives. A matrix can be composed of hydrophilic or hydrophobic carriers or combinations of both as incase of sustained release formulation. Potential hydrophilic carriers are polyethylene glycols (PEGs) (molecular weight >1000), polyvinyl alcohol, sugars (especially low melting-point sugars such as xylitol, dextrose, maltose and sorbitol), Gelucires of higher hydrophilic–lipophilic balance (HLB 14) values, water soluble polyoxyethylene derivatives (e.g., Brijs), polyethylene–propylene glycol copolymers (poloxamers), poly (ethylene oxide) (PEO) derivatives, PEG derivatives, PEG–PEO derivatives, or various combinations. When melted, these solids are completely immiscible with silicone oils, mineral oil, vegetable oils, aliphatic long-chain hydrocarbons, or various combinations. Commercially available silicone oils having a wide range of viscosities are most suitable as the liquid in the column. They are clear, nontoxic, non rancidifying, and predominantly inert.

Moreover, they have very low freezing points. The densities of molten, hydrophilic solids are usually higher than that of these liquids, so using Apparatus I to form pellets with these materials would be appropriate. Potential hydrophobic carriers include glyceryl monostearate, glyceryl palmitostearate (GPS), glyceryl dibehenate, ethylene glycol palmitostearate, cetostearyl alcohol, cetyl alcohol, stearyl alcohol, cholesterol, hydrogenated vegetable oils, phospholipids and its derivatives, lanolin, triglycerides, long-chain fatty acids or hydrocarbons, hard fat, oil-soluble Brijs, cocoa butter and other waxes, and combinations of these. When melted, these solids are completely immiscible with some hydrophilic liquids such as liquid PEGs (MW 200-600), propylene glycol, glycerin, ethyl alcohol and various combinations. These liquids can serve as cooling liquids. The densities of hydrophobic solids are usually lower than those of hydrophilic liquids, so using Apparatus II to form pellets would be appropriate. Some liquids are immiscible with both hydrophobic and

hydrophilic molten solids. This property allows them to serve as cooling liquids for sustained-release pellets containing mixtures of hydrophilic and hydrophobic solids [29, 31]. Examples include silicone oils with viscosities >20 cP that are immiscible with hydrophilic solids such as PEGs and certain hydrophobic solids such as glyceryl dibehenate and carnauba wax. **Table 2** and **3** lists the physical properties of some carrier solids and cooling liquids that can affect the freeze-pelletization process [31, 32].

Application of Freeze Pelletization: Freeze pelletization offers several advantages over other pelletization methods in terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution and solid at room temperature, so drying is not required. This technique has many potential applications in the preparation of both immediate and controlled release matrix pellets. To demonstrate the applicability of this technique, a variety of pellets were prepared including immediate release dexamethasone and theophylline pellets using PEG matrices in apparatus I, sustained release theophylline pellets using mixtures of PEG bases and waxes in apparatus I and sustained release theophylline and diltiazem HCl pellets using a variety of waxes in apparatus II. Immediate release pellet formulations containing dexamethasone and theophylline released 100% drug within 30 minutes. However, in the case of sustained release pellets, the release rates depended on the matrix type/composition, pellet size, aqueous solubility of the drug, drug loading and the presence of additives such as surfactants.

TABLE 2: PHYSICAL PROPERTIES OF SOME CARRIER SOLIDS THAT CAN AFFECT FREEZE PELLETIZATION TECHNIQUE

CARRIER SOLIDS	MELTING POINT (°C)	DENSITY (g/cm^3)	VISCOSITY (cP)
PEG 1000	37–40	1.15–1.21 at 25 °C	18–22 at 99 °C
PEG 1500	44–48	1.15–1.21 at 25 °C	30–38 at 99 °C
PEG 4000	50–58	1.15–1.21 at 25 °C	126–181 at 99 °C
PEG 6000	55–63	1.15–1.21 at 25 °C	287–448 at 99 °C
PEG 8000	60–63	1.15–1.21 at 25 °C	540–1035 at 99 °C
Gelucire 50/13	46–51	-	-
Gelucire 44/14	40–50	0.91 at 70 °C	-
Poloxamer 188	52–57	1.06 at 25 °C	-
PEG Stearates	37–47	-	-
Glyceryl monostearate	55–60	0.88 at 90 °C	21 at 90 °C
Glyceryl Palmito–stearate (Precirol ATO 5)	52–55	0.87 at 90 °C	17 at 90 °C
Xylitol	92–96	1.52 at 25 °C	-
Sorbitol	110–112	1.507 at 25 °C	-
Maltitol	148–151	-	-
Mannitol	166–168	1.514 at 25 °C	-
Trehalose	97	-	-
Carnauba wax	75–83	0.84 at 90 °C	43 at 90 °C
Microcrystalline wax (Petrolite 195)	60–90	0.79 at 90 °C	17 at 90 °C
Beeswax	56–60	0.82 at 90 °C	15 at 90 °C
Stearyl alcohol	56–60	0.80 at 90 °C	8 at 90 °C
Brij 35	33	1.05 at 20 °C	-
Brij 72	43	-	-

TABLE 3: PROPERTIES OF SOME LIQUIDS THAT CAN AFFECT FREEZE PELLETIZATION

Liquid in the column	Freezing point (°C)	Density (g/cm3) at 20-25 °C	Viscosity (cP) at 20-25 °C
Propylene glycol	-59	1.038	58
Glycerin	17.8	1.26	>110
PEG 300	-15 to -8	1.12	77
PEG 400	4–8	1.12	101
PEG 600	15–25	1.08	141
Almond oil	-18	0.91–0.915	-
Oleic acid	4	0.895	26
Castor oil	-12	0.957–0.968	1000
Mineral oil	-12 to -9	0.84–0.89	110-230

SUMMARY AND CONCLUSION: This review focused on novel hot-melt extrusion and freeze pelletization technique, recently reported to produce spherical pellets, eliminates problem associated with other techniques. Today melt extrusion technology represents an efficient pathway for manufacture of drug delivery systems. The potential of the technology is reflected in the wide scope of different dosage forms including oral dosage forms, implants, bioadhesive ophthalmic inserts and effervescent tablets. In addition, the physical state of the drug in an extrudate can be modified with the help of process engineering and by using various polymers. The possible use of a broad selection of polymers starting from high molecular weight polymers to low molecular weight polymers and various plasticizers has opened a wide field of numerous combinations for formulation research. Drawbacks of the technology are often related to high energy input mainly related to shear forces and temperature. The design of screw assemblies and extruder dies are two major areas, which have significant impact on product quality and degradation of drug and polymers. Drugs which are sensitive to elevated temperatures can be processed successfully when the residence time is short. Work in this field is increasing and the literature published reveals many novel and interesting aspects of this technology such as in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt, and nanoparticles released from molecular dispersions manufactured by melt extrusion. Freeze pelletization has many potential applications for preparing immediate- and controlled-release matrix pellets. Controlled-release pellets are matrix type and do not require additional coating. Pellets made using freeze-pelletization can be subsequently coated with suitable polymers to produce delayed-release and colon-specific formulations.

Various excipients can be used in this technique, and formulations can be easily modified to suit a wide range of drug delivery applications. Although the production rate of freeze pelletization may be lower than those of conventional industrial methods, it may not be a major limitation because of the significantly decreased time required to process the raw materials. It should be possible to scale-up this process by increasing the number of injectors (nozzles), to several hundred if required, to meet the desired rate of production. These injectors can be arranged in various configurations depending on the design of the apparatus, and they can be static or vibrated electrically. Using freeze pelletization, it should be possible to spray

the molten solid matrix with an atomizer instead of adding it drop-wise into the column to obtain micropellets.

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