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Controlled-Release Pelletized Dosage Forms Using the Extrusion-Spheronization Process

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ABSTRACT – Pellets, which are multiple-unit dosage systems, have the several therapeutic advantages over single-unit dosage systems in oral drug delivery. This review focuses on the current status and explores extrusion-spheronization technique with special attention to controlled-release application of pellets including coated pellets for delayed release formulations, coated pellets for colon delivery, coated pellets for sustained drug delivery, sustained-release matrix pellets, pellets compressed into tablets, bioadhesive pellets, floating pellets, and pelletization with solubilization techniques.

Key words – Pellets, Multiparticulates, Modified- release, Pelletization, Solubilization

Pelletization process is an agglomeration process that results in agglomerates of a narrow size distribution in the range of 0.5-1.5 mm with a low intra-agglomerate porosity (about 10%) and the higher density compared to the granules. Pellets are produced by pelletization process and these agglomerates have the relatively spherical shape, low friability and free flowing properties, which facilitate the handling of pellets in the manufacturing process. Pelletization process can prevent the segregation of co-agglomerated components, resulting in an improvement of the content uniformity. Pelletization process can also avoid the dust formation resulting in an improvement of the process safety, as fine powders can cause dust explosions and respiratory health problems. Pellets are widely used in multiparticulate systems and multiparticulate systems have the several therapeutic advantages over single-unit dosage systems in oral drug delivery. The low inter- and intra-subject variability can be achieved by multiparticulate systems because multiparticulates can pass through the pylorus immediately after administration. Moreover, less effect of food on drug absorption and rather uniform gastric emptying time than single-unit dosage systems can be attainable in multiparticulate systems. Safety concerns due to dose dumping of drugs, which have narrow therapeutic index, is minimized in multiparticulate systems, and more foreseeable drug delivery in sustained release formulation is possible because the total drug dose is divided over many units, not in a single-unit system. The small size of multiparticulates also enables them to be well dispersed along the gastrointestinal (GI) tract, enhancing drug absorption and reducing the irritant effect that single-unit systems may cause to the mucosal lining, especially if remained for an extended time at a specific site. The spherical pellets can be coated with rate-controlling polymers or compressed into tablets to achieve delayed-release, extended-release, and targeted-release profiles. Multiparticulate systems with different dose strengths can be obtained from the same batch of drug-loaded pellets without additional formulation or process modification. Pellets with different drugs or with different release profiles can be blended and formulated in a single-unit dosage form such as capsule, which promotes the delivery of two or more chemically compatible or incompatible drugs at the same or different sites in the GI tract.

Although several pelletization techniques such as high-shear, fluid-bed, spray-drying, and rotary-granulation techniques, are developed and available in the pharmaceutical industry, the extrusion-spheronization technique has certain advantages such as preparation of spherical pellets with uniform size and high-drug loading (up to 90%) at a moderate cost using minimum excipients. In various pelletization techniques, this review focuses on the current status and explores extrusion-spheronization technique with special attention to controlled release application of pellets. A thorough discussion of process variables for extrusion-spheronization or characterization of

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pellets is beyond the scope of this review, but the topic has been intensively reviewed elsewhere (Rahman et al., 2009; Sinha et al., 2009; Trivedi et al., 2007).

Manufacturing Process of Extrusion-Spheronization

The extrusion-spheronization technique involves five main steps: 1) dry mixing; 2) wet mixing; 3) extrusion; 4) spheronization; and 5) drying process. The extrusion-spheronization process for immediate/modified-release pellet formulations is outlined in Fig. 1. The main purpose of dry mixing is to obtain the homogenous mixtures of ingredients including drug and excipients. The drug and excipients were screened through a specific diameter sieve and mixed in a mixer. Several types of blenders can be used for dry mixing such as a planetary mixer, a sigma blade mixer, and a high shear mixer. A planetary mixer is the most widely used equipment for the extrusion-spheronization process (Freire et al., 2010; Mallipeddi et al., 2010; Pund et al., 2010; Zeeshan and Bukhari, 2010). After dry mixing in the blender, wet mixing is generally performed in the same mixer by spraying the liquid (binder solution). To achieve the desired extrudates, two factors are crucial in wet mixing process: 1) the amount of liquid which is added to the powder mixture to produce the wet mass; 2) the homogenous distribution of liquid throughout the powder bed (Trivedi et al., 2007). Extrusion is where the wet mass is forced to pass through a mold or die with an appropriate opening to produce cylinders or rod-shaped particles with uniform diameter known as extrudates. The properties of extrudates are affected by many process factors including screen pressure, screen hole diameter, extruder type, screw speed, and extrusion temperature. A spheronizer consists of a static cylinder cylindrical bowl with a bottom 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. The plate has a grooved pattern that is responsible for spheronizing the cylindrical extrudates. To create the spherical pellets, many processing parameters should be checked such as spheronization load, spheronization speed, spheronization time, spheronizer type, and plate type. A drying stage is essential to obtain the desired moisture content. Pellets obtained after spheronization are wet state, and can be dried at room temperature or at elevated temperature in a tray drier/oven or in a fluidized bed drier. As shown in Fig. 1, some additional processes may need to achieve controlled drug delivery systems. Solid dispersion or self-emulsifying mixtures of poorly water-soluble drugs may be used in wet mixing process

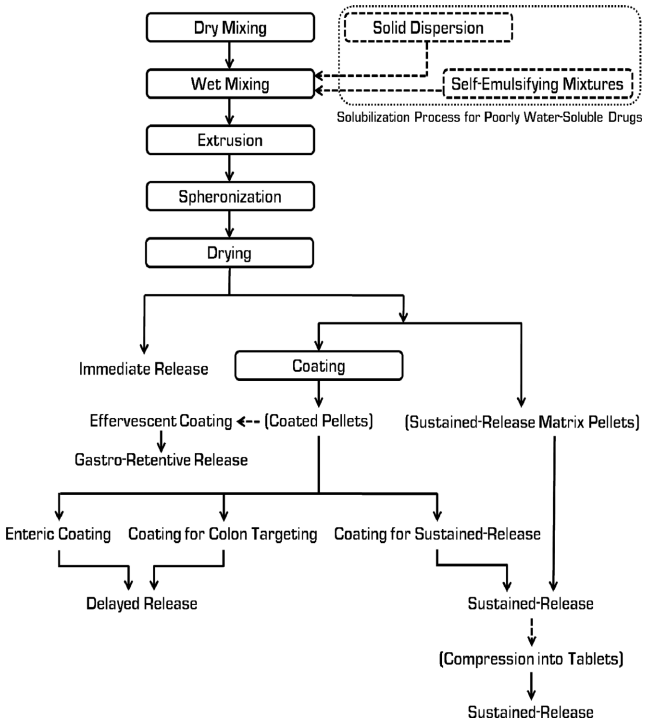

Figure 1. The extrusion-spheronization process for immediate/modified-release pellet formulations

to increase the drug dissolution rate, and appropriate coating polymers can be utilized for the pellet coating process.

Controlled-Release Application of Pellets

The pellets prepared by extrusion-spheronization technique have been widely investigated in the field of pharmaceutical drug delivery science and various modified-release pellet systems are developed and introduced. With regard to the final dosage form, the pellets can be filled into hard capsules or be compressed into tablets. The film coating or tableting of pellets can be used to obtain the modified-release of drugs from the pellets because generally, the pellets prepared by extrusion-spheronization technique do not have modified-release properties. Recently, bioadhesive pellets and floating pellets have created new possibilities for the site-specific application of drug compounds. Moreover, pellet systems containing solid dispersion or self-emulsifying mixture have been introduced to increase the dissolution rate of poorly water-soluble drugs.

Modified-release dosage forms

Coated pellets for delayed release formulations

Enteric coatings play an important role in protecting drugs that are decomposable in the stomach by low pH or enzymatic degradation. Enteric coating is also undertaken to prevent gas-

tric irritation in individuals which often follows the administration of irritating compounds such as non-steroidal anti-inflammatory drugs (NSAIDS). Enteric coating dissolves in the neutral or alkaline fluids of the intestine and the drugs become available for absorption into the blood stream.

Many reports have been published on enteric coated pellets (Bendas and Ayres, 2008; Bruce et al., 2003; Chivate and Poddar, 2008; Kilor et al., 2010; Liu et al., 2003; Shavi et al., 2009; Williams and Liu, 2000; Zhang et al., 2009), and examples of pellet formulations prepared by enteric coating method are shown in Table I. As shown in Table I, Eudragit® L 100-55 (Eudragit® L 30 D-55) and triethyl citrate were widely used as a coating material and plasticizer, respectively. The influence of polymeric subcoats and organic acids on the dissolution properties of enteric coated sodium valproate pellets was evaluated, and delay in drug release was observed when citric acid was present in a HPMC subcoat or when added to the core pellet formulation due to lowering the pellet micro-environmental pH and reduced pellet core solubility as a result of conversion of the sodium valproate to valproic acid (Bruce et al., 2003). The enteric coated pellets containing a mixture of proteolytic enzymes were prepared to prevent the drug degradation in the acidic environment, and to achieve better bioavailability (Chivate and Poddar, 2008). To reduce the gastric side effect of aceclofenac, enteric coating was performed in aceclofenac pellets with Eudragit® L 100-55 (Kilor et al., 2010; Shavi et al., 2009). Moreover, the modified drug release profiles can be achieved by the application of enteric-coated pellet formulation (Bendas and Ayres, 2008; Williams and Liu, 2000; Zhang et al., 2009).

Table I. *Examples of Pellet Formulations Prepared by Enteric Coating Method*

Drugs	Excipients for core pellets	Coating materials	Plasticizer	Ref.
Theophylline	Avicel PH 101, Lactose	Aquacoat® CPD	Diethyl phthalate	(Williams and Liu, 2000)
Valproate sodium	Avicel PH 101	Eudragit® L 30 D-55	Triethyl citrate	(Bruce et al., 2003)
Theophylline	Avicel PH 101	Eudragit® L 30 D-55	Triethyl citrate	(Liu et al., 2003)
Ranitidine HCl	Avicel PH 101	Eudragit® L 30 D-55	Triethyl citrate	(Bendas and Ayres, 2008)
Proteolytic enzymes	Avicel PH 101	Eudragit® L 100-55	Triethyl citrate	(Chivate and Poddar, 2008)
Aceclofenac	Avicel PH 101, Lactose	Eudragit® L 100-55	PEG 6000	(Shavi et al., 2009)
Tamsulosin hydrochloride	Avicel PH 101, Lactose	Eudragit® L 30 D-55	PEG 6000	(Zhang et al., 2009)
Aceclofenac	MCC, Lactose, κ-Carrageenan, Starch	Eudragit® L 100-55	Triethyl citrate	(Kilor et al., 2010)

Avicel PH 101, MCC: Microcrystalline cellulose; Aquacoat® CPD: Cellulose acetate phthalate (CAP) aqueous dispersion; Eudragit® L 30 D-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent" Ph. Eur.; Eudragit® L 100-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A" Ph. Eur.Table II. Examples of Pellet Formulations for Colon Delivery

Table II. *Examples of Pellet Formulations for Colon Delivery*

Drugs	Main excipients for core pellets	Coating materials	Ref.
Ibuprofen	Avicel PH 101, Mannitol, Citric acid monohydrate	Aqoat™, AS-HF	(Krogars et al., 2000)
Lactobacilli	Avicel PH 101, Lactose	Eudragit® FS 30 D	(Brachkova et al., 2009)
Mesalamine	Gelucire® 44/14, Kollidon® 90 F	Eudragit® S 100	(Chuong et al., 2009)
Mesalamine	Avicel PH 101	Nutriose®, Aquacoat® ECD-30	(Karrout et al., 2009)
Mesalamine	Gelucire® 44/14, Kollidon® 90 F	Eudragit® S 100, Eudragit® FS 30 D, Eudragit® L 100-55	(Bendas et al., 2010)
Mesalamine	Avicel PH 101	Hylon® V, Hylon® VII, IM-DS acetate starch, LAPS, Surelease®	(Freire et al., 2010)

Avicel PH 101, MCC: Microcrystalline cellulose; Gelucire® 44/14: Lauroyl Macrogolglycerides (Polyoxylglycerides); Kollidon® 90 F: Polyvinylpyrrolidone (K-value: 81.0-96.3); Eudragit® FS 30 D: the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid; Aqoat™ AS-HF: Hydroxypropyl methylcellulose acetate succinate (HPMCAS); Eudragit® S 100: "Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)" Ph. Eur.; Nutriose®: Water-soluble, branched dextrin with high fiber contents; Aquacoat® ECD-30: 30% (w/w) aqueous dispersion of ethylcellulose; Eudragit® L100-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A" Ph. Eur.; Hylon® V: High-amylose maize starch (amylose contents of 56%); Hylon® VII: High-amylose maize starch (amylose contents of 69%); IM-DS acetate starch: Acetylated form of Hylon VII with a degree of substitution of 1.5 and an amylose content of 71%; LAPS: Low-amylopectin maize starch; Surelease®: Aqueous ethylcellulose dispersions

Coated pellets for colon delivery

In the site-specific drug delivery to the colon, multi-particulate pellets are preferable dosage forms compared with single unit dosage forms (e.g., tablets or capsules) because 1) the all-or-nothing effect can be avoided; 2) the less fluctuated gastric emptying time is obtainable; 3) highly dosed drugs can be incorporated in the core of coated pellets.

Examples of pellet formulations for colon delivery are listed in Table II. Various polymers such as HPMCAS (Krogars et al., 2000), methacrylic acid-methyl methacrylate copolymer (Bendas et al., 2010; Brachkova et al., 2009; Chuong et al., 2009), branched dextrin (Karrout et al., 2009), ethylcellulose (Freire et al., 2010; Karrout et al., 2009), and amylose maize starch (Freire et al., 2010) were applied to the colon-specific drug delivery, and in many cases, mesalamine (5-aminosalicylic acid) was used as the model drug for the local treatment of inflammatory bowel diseases (Bendas et al., 2010; Chuong et al., 2009; Freire et al., 2010; Karrout et al., 2009).

Coated pellets for sustained drug delivery

Coating is the most commonly accepted methods for obtaining sustained drug release from pellets. Pellet coating with rate-controlling polymers in a fluid-bed coater is an approach to develop the sustained-release dosage forms. Surface properties and sphericity of pellets are crucial factors in accomplishing a consistent coating around the pellets. Sufficient mechanical strength of pellets is another critical factor for coating process because breakage of pellets during the fluidization process can be avoided by acceptable mechanical strength of pellets.

Table III lists examples of sustained-release pellet formulations by coating method. Indomethacin extended release formulation was developed by extrusion-spheronization method, and the drug containing pellets were further coated with EC, HPMC, or Eudragit® RL 100 to achieve the required release profile. Desired and reproducible results were achieved via microporous membrane coating using a soluble salt like sodium lauryl sulfate in the film coating solution (Elchidana and Deshpande, 1999). Huang et al. have shown that the hygroscopic character of pyridostigmine bromide can be improved by coating process and the sustained-release pellets with specific release rate can be achieved by sustained-release coated pellets (Huang et al., 2007). Scala-Bertola et al. have investigated the pellet formulations containing two low-molecular-weight heparins, enoxaparin or bemiparin with Eudragit® RS 30 D coating for oral delivery. The authors have reported that low-molecular-weight heparin in a pellet dosage form may offer a more convenient and industrializable way of manufacture leading to an easier scale-up process (Scala-Bertola et al., 2009).

Sustained-release matrix pellets

Sustained-release matrix pellets are preferred to sustained-release coated pellets because of their ease of manufacture and in-process control. Theoretically, sustained-release matrix pellets can be formulated via the extrusion-spheronization process. However, the main difficulties of sustained-release matrix pellets are associated with large surface area of pellets, amount of drug loading in pellets and high water-absorption capacity

Table III. *Examples of Sustained-Release Pellet Formulations by Coating Method*

Drugs	Main excipients for core pellets	Coating materials	Ref.
Indomethacin	MCC, Mannitol, Lactose	EC, HPMC, Eudragit® RL 100	(Elchidana and Deshpande, 1999)
Theophylline	Avicel PH 101	Eudragit® NE 30 D	(Liu et al., 2003)
Pyridostigmine bromide	Avicel pH 102	Surelease®	(Huang et al., 2007)
Theophylline	Avicel PH 101	Eudragit® RS 30 D, Pectin-chitosan polyelectrolyte complex	(Ghaffari et al., 2008)
Venlafaxine HCl	Avicel PH 101	Eudragit® NE 30 D	(Tian et al., 2008)
Ambroxol HCl	Avicel PH 101, Lactose	Eudragit® RL 30 D, Eudragit RS 30 D	(Kibria et al., 2009)
Enoxaparin, Bemiparin	Avicel PH 101, Lactose	Eudragit® RS 30 D	(Scala-Bertola et al., 2009)
Tamsulosin hydrochloride	Avicel PH 101, Lactose	Eudragit® NE 30 D	(Zhang et al., 2009)
Gliclazide	Avicel PH 101, EC	Eudragit® NE 30 D, Eudragit® L 30 D-55	(Wang et al., 2010a)

Avicel PH 101, Avicel PH 102, MCC: Microcrystalline cellulose; EC: Ethylcellulose; Eudragit® RS 30 D: Aqueous dispersions of Eudragit® RS 100 with 30% dry substance (6.11-8.26 % ammonio methacrylate units on dry substance); Eudragit® NE 30 D: "Polyacrylate Dispersion 30 Per Cent" Ph. Eur.; Eudragit® L 30 D-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent" Ph. Eur.; HPMC: Hydroxypropyl methylcellulose; Eudragit® RL 100: "Ammonio Methacrylate Copolymer Type A" Ph. Eur. (8.9-12.3% ammonio methacrylate units on dry substance), granule type; Surelease®: Aqueous ethylcellulose dispersions; Eudragit® RL 30 D: Aqueous dispersions of Eudragit® RL 100 with 30% dry substance (10.18-13.73 % ammonio methacrylate units on dry substance)

Table IV. *Examples of Sustained-Release Matrix Pellet Formulations*

Drugs	Main excipients for matrix pellets	Ref
Theophylline	Gelucire® 50/02, Gelucire 55/18, Avicel CL 611	(Montousse et al., 1999)
Thiazole-based leukotriene D_4 antagonist	Eudragit® L 100-55, Eudragit® S 100	(Mehta et al., 2000, 2001)
Theophylline	EC, HPMCAS	(Kojima and Nakagami, 2002)
Theophylline	Gelucire® 50/02	(Siepmann et al., 2006)
Theophylline	Powdered cellulose, PVP, poly(N-isopropyl acrylamide)	(Mayo-Pedrosa et al., 2007)
Ambroxol HCl	Compritol® 888 ATO, EC	(Chi et al., 2010)

Gelucires® 50/02: Mixture of mono-, di- and triglycerides and polyethylene glycol esters; Gelucires® 55/18: Polyethylene glycol stearates; Avicel CL 611: Co-processed microcrystalline cellulose and 13.5-16.4% sodium carboxymethyl cellulose; Eudragit® L 100-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A" Ph. Eur.; Eudragit® S 100: "Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)" Ph. Eur.; EC: Ethylcellulose; HPMCAS: Hydroxypropyl methylcellulose acetate succinate; PVP: Polyvinylpyrrolidone; Compritol® 888 ATO: Glyceryl behenate Table V. Examples of Pellet Formulations Compressed into Sustained-Release Tablets

Table V. *Examples of Pellet Formulations Compressed into Sustained-Release Tablets*

Drugs	Main excipients for pellets	Coating materials	Ref.
Ketoprofen	Avicel PH 101	Eudragit® NE 30 D, Guar gum	(el-Mahdi and Deasy, 2000)
Piroxicam	Avicel PH 101, Avicel RC 581, Avicel CL 611	Eudragit® L 30 D-55, Eudragit® FS 30 D	(Debunne et al., 2002)
Diltiazem	MCC, Glyceryl monostearate	-	(Panchagnula et al., 2006)
Ibuprofen	Eudragit® RS PO, Eudragit® RL PO, Avicel PH 101	-	(Abbaspour et al., 2007)
Pseudoephedrine HCl	MCC	Eudragit® RS-30 D, Kollicoat® SR-30 D, HPMC	(Zeeshan et al., 2009)
Loratadine, Pseudoephedrine HCl	MCC	Kollicoat® SR-30 D, HPMC	(Zeeshan and Bukhari, 2010)

Avicel PH 101: Microcrystalline cellulose; Avicel RC 581: Co-processed microcrystalline cellulose and 8.3-13.8% sodium carboxymethyl cellulose; Avicel CL 611: Co-processed microcrystalline cellulose and 13.5-16.4% sodium carboxymethyl cellulose; MCC: Microcrystalline cellulose; Eudragit® RS PO: "Ammonio Methacrylate Copolymer Type B Ph. Eur. (4.5-7.0% ammonio methacrylate units on dry substance), powder type; Eudragit® RL PO: "Ammonio Methacrylate Copolymer Type A "Ph. Eur. (8.9-12.3% ammonio methacrylate units on dry substance), powder type; Eudragit® NE 30 D: "Polyacrylate Dispersion 30 Per Cent" Ph. Eur.; Eudragit® L 30 D-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent" Ph. Eur.; Eudragit® FS 30 D: the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid; Eudragit® RS 30 D: Aqueous dispersions of Eudragit® RS 100 with 30% dry substance (6.11-8.26 % ammonio methacrylate units on dry substance); Kollicoat® SR-30 D: Polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate

of microcrystalline cellulose, which was used as a spheronization aid. Examples of sustained-release matrix pellet formulations are listed in Table IV.

Several hydrophobic materials have been reported to achieve sustained-release matrix pellets. Waxes such as Gelucires (Montousse et al., 1999; Siepmann et al., 2006) and Compritol 888 ATO (Chi et al., 2010) were used for theophylline and ambroxol sustained-release matrix pellets. Hydrophobic polymer such as ethylcellulose (Chi et al., 2010; Kojima and Nakagami, 2002; Mayo-Pedrosa et al., 2007) and enteric-coated polymer such as Eudragit® L 100-55 (Mehta et al., 2000, 2001) were also utilized for sustained-release matrix pellets.

Pellets compressed into tablets

Despite several advantages of multiparticulate systems, monolithic systems are preferred to ensure patient compliance and dosing accuracy. In addition, the advantages of tableting multiparticulates include a reduce risk of tampering, higher dose strength with compacted size, lower cost and higher output rates than pellet-filled capsules, less sensitive to moisture, and more flexible dosing regimen (Bodmeier, 1997). Because the polymeric coating must be able to withstand the compression force and should not lose the controlled release properties, the tableting of sustained-release coated pellets is more challenging than the compression of traditional powder mixtures. Strategies to retain the sustained-release property of the pellets during compaction include increased thickness (Sawicki and Lunio, 2005), reduction in the tablet surface area (Wagner et al., 2000), the utilization of highly flexible films (Dashevsky et al., 2004), or the application of cushionable additives (Debunne et al., 2002; Vergote et al., 2002). When compared to the ethylcellulose films, films prepared from

acrylic polymers are more flexible and therefore more suitable for the coating of pellets to be compressed into tablets (Bodmeier, 1997).

Examples of pellet formulations compressed into sustained-release tablets are shown in Table V. As listed in Table V, methacrylate copolymers (Eudragit®) were widely used for coating materials of pellets compressed into tablets. Abbaspour et al. developed matrix tablet containing ibuprofen by compressing matrix pellets (Abbaspour et al., 2007). The authors compared the physicomechanical and release properties of thermal treated (cured) pellets with those of uncured pellets in an attempt to identify those pellets able to withstand the compression process. The authors revealed that thermal treating is a proper tool to produce plastic ibuprofen pellets based on Eudragit® RS PO and Eudragit® RL PO, and this plastic behavior can probably prevent damage to the cores or their coating under the compression.

Gastro-retentive systems

Bioadhesive pellets

The production of bioadhesive pellets containing polyacrylic acids could be of interest for site-specific targeting of drugs, because this form of administration associates the advantages of a multiparticulate carrier with potentially greater predictability and reproducibility of therapeutic effects, and a mucoadhesive carrier allowing the localization of the drug at the site of absorption (Mezreb et al., 2004). Table VI lists examples of bioadhesive pellets and floating pellets. To obtain bioadhesive pellets, Awad et al. developed the preparation method of bioadhesive pellets using polyacrylic acids (Noveon® AA1, Carbopol® 974P and Carbopol® 971P) by extrusion-spheronization method without any electrolyte, which might affect the bioadhesive properties of the polymers used (Awad et al., 2002). Mezreb et al. evaluated three process variables—extrusion speed, spheronizer speed, and spheronization time—to optimize extrusion-spheronization process for the preparation of bioadhesive pellets (Mezreb et al., 2004). These authors concluded that these pellets will preferentially adhere to regions in the gastrointestinal tract having a pH ranging from 6.2 to 6.6 (duodenum) rather than those with a higher pH (Awad et al., 2002; Mezreb et al., 2004).

Floating pellets

It is well recognized that gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms. Floating drug delivery system is one of gastro-retentive dosage forms which could extend GRT to accomplish sufficient drug bioavailability. To achieve the floating drug delivery system, low density system or gas-generating system can be used (Sungthongjeen et al., 2006; Wiwattanapatapee et al., 2004). Wiwattanapatapee et al. have investigated low density floating pellets containing viable endospores of *Bacillus megaterium* using hydrogenated vegetable oil although the target of pellets is not for human use (Wiwattanapatapee et al., 2004). The authors evaluate the physical characteristics of the formulations, and bacterial release from pellets. In conclusion, these products performed good floating property and released bacteria over time. Sungthongjeen et al. developed a new floating pellets based on gas formation technique (Sungthongjeen et al., 2006). The spherical drug-containing core pellets was prepared by extrusion–spheronization process followed by coating of the pellets with effervescent component (sodium bicarbonate) using hydroxypropyl methylcellulose (HPMC) as a binder and gas-

Table VI. *Examples of Bioadhesive Pellets and Floating Pellets*

Type	Drugs	Main excipients for pellets	Mechanism	Ref.
BP	Caffeine	Noveon® AA1, Carbopol® 974P, Carbopol® 971P, Avicel PH 101	Bioadhesive property of polyacrylic acids	(Awad et al., 2002)
BP	-	Carbopol® 974P, Carbopol® 971P, Avicel PH 101	Bioadhesive property of polyacrylic acids	(Mezreb et al., 2004)
FP	Bacillus megaterium	Hydrogenated vegetable oil, Lactose, Avicel PH 101	Low density excipient	(Wiwattanapatapee et al., 2004)
FP	Theophylline	Avicel PH 101 (Core pellets)	Gas generating system	(Sungthongjeen et al., 2006)
		Sodium bicarbonate (inner effervescent coating layer) Eudragit® RL 30 D, RS 30 D or NE 30 D (outer gas-entrapped polymeric coating layer)		

BP: Bioadhesive Pellet; FP: Floating Pellet

Noveon AA1: Polycarbophil (homopolymer of acrylic acid cross-linked with divinylglycol); Carbopol 974P: "Carbomer Homopolymer Type B", USP/NF; Carbopol 971P: "Carbomer Homopolymer Type A", USP/NF; Avicel PH 101: Microcrystalline cellulose; Eudragit® RL 30 D: Aqueous dispersions of Eudragit® RL 100 with 30% dry substance (10.18-13.73% ammonio methacrylate units on dry substance); Eudragit® RS 30 D: Aqueous dispersions of Eudragit® RS 100 with 30% dry substance (6.11-8.26% ammonio methacrylate units on dry substance); Eudragit® NE 30 D: "Polyacrylate Dispersion 30 Per Cent" Ph. Eur.

entrapped polymeric membrane (Eudragit® RS 30D, RL 30D, NE 30D), respectively. The floating ability and drug release of the system were dependent on amount of the effervescent agent layered onto the core pellets, and type and coating level of the polymeric membrane. Only Eudragit® RL 30 D membrane system could float. The floating pellets with sustained drug release were obtained and could be a promising gastroretentive formulation.

Pelletization with solubilization techniques

Solid dispersion

The solid dispersion was defined as the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method (Chiou and Riegelman, 1971). Solid dispersions can be used to increase the dissolution rate of poorly soluble drugs, and they have proven to increase the amount of dissolved drug at the absorption site. Examples of pellet formulations containing solid dispersion or self-emulsifying mixtures are listed in Table VII.

According to the Biopharmaceutical Classication System, NSAIDs are regarded as a class II compound characterized by low water solubility and high permeability. Thus, low water solubility is major problem with this potentially useful drug candidate. For class II drugs, bioavailability is limited by their dissolution rate and can be increased by improving dissolution rate. Another major problem associated with NSAIDs is gastrointestinal irritation after oral administration. Therefore, there is a need for a formulation that is not only providing improvement in solubility but at the same time reducing the gastrointestinal adverse effects of NSAIDs. These objectives can be achieved by pellet formulations containing solid dispersion of NSAIDs such as ketoprofen (Jachowicz et al., 2000) and piroxicam (Pieszczek and Jachowicz, 2010) because multiparticulate pellet systems ensure less irritation of the gastrointestinal tract and a lower risk of side effects (Fekete et al., 1998). Controlled-release pellet formulations containing solid dispersion of nifedipine, which is one of the poorly water-soluble drugs, were also successfully developed, characterized, and evaluated by Mehta et al. (Mehta et al., 2002).

Self-emulsifying pellets

Microemulsions have been intensively studied to enhance the bioavailability of the poor water-soluble drugs (Talegaonkar et al., 2008). For oral drug delivery, a self emulsifying drug delivery system (SEDDS) has been widely used because it is easy to formulate as soft or hard capsules (Gursoy and Benita, 2004). SEDDS is an anhydrous pre-concentrated system of microemulsion, which is composed of oil, surfactant or cosurfactant, and SEDDS is capable of self-emulsification after coming into contact with the physiological fluids on ingestion under gentle agitation. After oral administration, SEDDS can maintain the poorly soluble drugs dissolved in the fine oil droplets when transiting through the gastrointestinal

Table VII. *Examples of Pellet Formulations Containing Solid Dispersion or Self-Emulsifying Mixtures*

Type	Drugs	Components of SD or SE mixtures	Main excipients for pellets	Ref.
SD	Ketoprofen	KLH_T, PEG 4000, 6000, 9000	Avicel PH 101, Lactose	(Jachowicz et al., 2000)
SD	Nifedipine	Pluronic F-68	Eudragit L 100-55, Eudragit S 100	(Mehta et al., 2002)
SD	Piroxicam	Meglumine	Avicel PH 101, Lactose	(Pieszczek and Jachowicz, 2010)
SE	Progesterone	Imwitor® 742, Polysorbate 80	Avicel PH 101	(Tuleu et al., 2004)
SE	Diazepam	Cithrol GMS®, Solutol® HS 15	Avicel PH 101	(Abdalla and Mader, 2007)
SE	Methyl/Propyl paraben	Imwitor® 742, Polysorbate 80	Avicel PH 101, Lactose	(Serratoni et al., 2007)
SE	Progesterone	Solutol® HS 15, Captex® 355, Capmul® MCM	Avicel PH 101	(Abdalla et al., 2008)
SE	Vinpocetine	Akoline MCM, Polysorbate 80, Peanut oil	Microcel 101, Lactose	(Iosio et al., 2008)
SE	Nitrendipine	Miglyol® 812, Transcutol® P, Polysorbate 80, Cremophor® RH 40	Kollidon CL-SF, Syloid 244 FP, Avicel PH 101, Lactose	(Wang et al., 2010b)

SD: Solid Dispersion; SE: Self-Emulsifying Drug Delivery System

KLH_T: N-cocoyl-protein condensate sodium salt; PEG: Polyethylene glycol; Avicel PH 101, Microcel 101: Microcrystalline cellulose; Pluronic F-68: Poloxamer 188; Polysorbate 80: Polyoxyethylene sorbitan fatty acid esters; Imwitor 742®, Akoline MCM: Mono- and diglycerides; Cithrol GMS®: Glyceryl Stearate; Solutol® HS 15: Macrogol-15-hydroxystearate; Captex® 355: Triglycerides of caprylic/capric acid; Capmul® MCM: Medium chain mono- and di-glycerides; Miglyol® 812: Caprylic/capric triglyceride; Transcutol® P: Diethylene glycol monoethyl ether; Cremophor® RH 40: PEG-40 hydrogenated castor oil; Eudragit® L 100-55: "Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A" Ph. Eur.; Eudragit® S 100: "Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)" Ph. Eur.; Kollidon® CL-SF: Crospovidone; Syloid® 244 FP: Porous silicon dioxide

tract. Advantages associated with SEDDS for oral delivery include improvement in oral bioavailability, reduction in inter-subject and intra-subject variability, reduction of food effects, and ease of manufacturing and scale-up (Ghosh and Murthy, 2006). Despite various advantages of microemulsions, traditional preparations of SEDDS are usually prepared in the liquid state, and the liquid SEDDS are generally enclosed by soft or hard capsules to facilitate oral administration. However, some disadvantages of liquid formulation include high production costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing (Wang et al., 2010b). To overcome these problems, the idea of combining the advantages of SEDDS with pellets through the inclusion of a self-emulsifying mixture into microcrystalline cellulose and the production of pellets using extrusion-spheronization was introduced by Newton et al. (Newton et al., 2001). As shown in Table VII, many hydrophobic drugs were developed to pellet formulations, and the incorporation of the self-emulsifying mixture into a solid dosage form is still challenging because self-emulsifying properties are more difficult to achieve with solid materials (Abdalla and Mader, 2007).

Conclusions

This review focused on the extrusion-spheronization process for immediate/modified-release pellets and controlled-release application of pellets including modified-release dosage forms, gastro-retentive systems, and pelletization with solubilization techniques. Extrusion spheronization is widely used method for producing spherical pellets with high drug loading (more than 90%), and the film coating or tableting of pellets can be utilized to achieve the modified-release of drugs from the pellets. Moreover, pelletization for gastro-retentive delivery is still a niche area of research, and several studies have been reported. The integration of extrusion-spheronization process and other drug delivery technology has the potential to improve therapeutic effects of drugs and emphasizes the capabilities of novel application of pellet systems.

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