Dry coating of solid dosage forms: an overview of processes and applications

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Abstract

Dry coating techniques enable manufacturing of coated solid dosage forms with no, or very limited, use of solvents. As a result, major drawbacks associated with both organic solvents and aqueous coating systems can be overcome, such as toxicological, environmental and safety-related issues on one hand as well as costly drying phases and impaired product stability on the other. The considerable advantages related to solventless coating has been prompting a strong research interest in this field of pharmaceutics. In the present article, processes and applications relevant to techniques intended for dry coating are analyzed and reviewed. Based on the physical state of the coat-forming agents, liquid- and solid-based techniques are distinguished. The former include hot-melt coating and coating by photocuring, while the latter encompass press coating and powder coating. Moreover, solventless techniques, such as injection molding and 3D printing by fused deposition modeling, which are not purposely conceived for coating, are also discussed in that they would open new perspectives in the manufacturing of coated-like dosage forms.

Keywords: dry coating, hot-melt coating, photocuring, press coating, powder coating, thermal adhesion coating, liquid-assisted coating, electrostatic coating, injection-molding, fused deposition modeling 3D printing

List of substance acronyms

AMG	acetylated monoglyceride
EC	ethyl cellulose
GMS	glyceryl monostearate
HEC	hydroxyethyl cellulose
HPC	hydroxypropyl cellulose
HPMC	hydroxypropyl methylcellulose
HPMCAS	hydroxypropyl methylcellulose acetate succinate
PEG	polyethylene glycol
PEO	polyethylene oxide
PVP	polyvinylpyrrolidone
TEC	triethyl citrate

1. Introduction

Manufacturing of coated solid dosage forms entails the deposition of different materials onto substrate cores, such as powder, granules, pellets, tablets and capsules, with the aim of achieving superior organoleptic and aesthetic characteristics, providing physical and chemical protection or modifying the drug release profile.

Conventional coating techniques, carried out by fluid bed or rotating pan equipment, involve spraying of a solution or suspension of the coating material(s) in an organic and/or aqueous vehicle, which generally represents not less than 70% w/w of the composition [1].

The use of organic solvents was preferred in the past as it enables shorter processing times and straightforward film formation. In more recent times, increasingly strict toxicological, environmental and safety-related requirements have led to progressive replacement of organic solvent- with aqueous-based coating, which may lower the overall manufacturing costs. Nevertheless, aqueous systems involve long and expensive drying phases, to remove the large amounts of water used, and frequently bring about stability issues. Indeed, because water migration may occur during the coating process or within storage, aqueous systems turn out unsuitable not only when moisture-sensitive bioactive compounds are dealt with, but also when the overall quality of the final product may be affected by humidity.

Hence, in view of the many issues associated with the use of solvents of whatever nature, alternative procedures or novel applications of well-established ones have been proposed over the years to improve pharmaceutical coating. Techniques that are generally referred to as “solventless” or “dry coating” include manufacturing methods that completely avoid solvents or at least markedly reduce the solvent to coating material ratio [2–4].

Notably, amounts of liquid <50% w/w on the solid material have long been employed in powder deposition processes, such as sugar coating derived from confectionary industry. This also applies to the layering of solid drugs onto inert seeds, wherein aqueous binding formulations are added to promote particle adhesion and cohesion. An attempt to exploit the powder layering technique for coating has recently been described. In this case, a swellable/erodible polymer (HPMC) powder was applied to drug-containing tablets for the manufacturing of a coated oral delivery system for time-controlled release [5].

Techniques that would properly be identified as dry coating processes may be classified relying on the physical state of the coat-forming agents when applied onto the substrate (Figure 1) [6]. Accordingly, liquid- or solid-based techniques are distinguished in this review article. In the first ones, melts or liquid precursors applied to the core surface are consolidated by cooling (hot-melt coating) or polymerization (coating by photocuring), respectively, to give a continuous layer. In

solid-based techniques, the coating material is directly applied to the substrate by compression (press coating), or else it can be layered and simultaneously consolidated by heating (powder coating). When layering is performed, the process can be improved, especially as regards the initial deposition phases, by spraying liquid aids and/or through the use of electrically charged powder particles.

In addition, innovative solventless techniques based on hot processing of thermoplastic materials allow the manufacturing of core+shell systems or of capsular devices comprising a functional shell and an inner drug formulation. Although not attained through any standard coating procedures, both such dosage forms may be regarded as "coated-like", and specific examples are reviewed in this article.

2. Liquid-based techniques

2.1. Hot-melt coating

In hot-melt coating processes, low-melting materials are deposited in the liquid state onto the surface of the cores, generally by spraying, and subsequently congealed in a controlled manner [7]. Such operations are commonly carried out by rotating pan or fluid bed for the manufacturing of coated pellets and granules. When the coating material is sprayed, it needs to be maintained at 40–60°C above its melting point [2,7,8]. The temperature represents the most critical process parameter and has to strictly be controlled in any part of the equipment. For this reason, the tubes through which the molten materials are conveyed from the reservoir to the spray nozzle have to be heated and/or properly insulated to prevent undesired cooling and consequent plugging. Moreover, nozzles purposely devised for spraying of melts may be needed. In particular, a triaxial nozzle structure comprising a central tube for supply of the coating agent, surrounded by a cavity for nebulizing air flow, enclosed within a further cavity for heated compressed air has been described (Figure 2) [9]. The nozzle should also be insulated to prevent re-melting of the applied coating upon contact of the units with its hot surface. Besides, it should correctly be located in the processing chamber thus enabling efficient deposition of droplets.

As a general rule, the spray rate has to be remarkably lower and more strictly controlled in hot-melt as compared with solvent-based coating, in order to achieve homogeneous distribution of the coating material and avoid agglomeration of the units. On the other hand, the overall processing time can be much shorter because no solvent removal is required. Indeed, the formula of the sprayed material corresponds to that of the final coating.

Easy flowing and sprayability of the melt are fundamental requisites for an excipient to be selected as a coating agent. These characteristics are generally satisfied by materials having <80°C melting point and <300 cps melt viscosity [2].

An alternative to spraying of the coating agent is represented by its direct addition to the core bed in the form of solid particles, thus having it melted *in situ* [10–13]. Subsequent cooling allows the melt deposited to solidify. In this case, reduction of equipment costs and simplified setup as well as cleaning operations are in principle possible, because spraying devices, thermostatic jackets and other related appliances are not required. The use of a hot air operated venturimeter has also been proposed to simultaneously fluidize core granules and a low-melting coating agent [14–16]. In this equipment, hot air is injected into a pipe, which aspires, by Venturi effect, the blend of solid materials introduced by a vibrating funnel, thus providing automatic feeding of the device. The blend, driven by a non-turbulent flux of air, moves forward within a thermostated path, along which melting of the coating material occurs, mainly at the particle surface. Subsequent falling of the cores at room temperature enables formation of a continuous coating by re-solidification.

In hot-melt coating, fatty acids, partially hydrogenated vegetable oils, glycerol esters, waxes and PEGs have broadly been employed [9,17]. A critical issue in the use of lipid coating agents of plant or animal origin is batch-to-batch reproducibility of their physico-chemical characteristics, which may affect consistency of processing and product performance.

Hot-melt coating has mainly been used for the production of prolonged-release formulations [11,12,18–22]. Nonetheless, taste-masked or moisture-protected dosage forms for immediate release have also been obtained [10,13,23,24].

In Table I, the main pharmaceutical applications of hot-melt coating and relevant process details are summarized.

2.2. Coating by photocuring

Photocuring, also known as light-curing or polymerization coating, provides a chemical approach to the attainment of coating layers exploited in many industrial fields and for medical applications [2]. It involves polymerization of functionalized liquid precursors (pre-polymers or monomers) in the presence of an initiator or a photosensitizer, and takes place at room temperature or below, resulting in rapid formation of a cross-linked network. This reaction is triggered by UV or visible light and may be based on free radical, cationic or anionic mechanisms depending on the nature of the precursors and initiators used. Equipment for photocuring needs to be provided with a light source, and a nitrogen purging system may also be necessary when the outcome of coating would be impaired by the presence of oxygen in the reaction environment.

A major advantage of photocuring over other solventless techniques is the possibility of operating at relatively low temperatures within short processing times, making this coating method appropriate for heat-sensitive compounds. However, photocuring appears to have a narrow potential for application in the pharmaceutical field on account of toxicological constraints, poor availability of proper starting materials and unsuitability for use in the case of photosensitive drug molecules. Indeed, only few examples of coating by photocuring are described in the literature. A number of these concerns UV light-induced coating of pellets with siloxane materials, which required the incorporation of various solid pore forming agents for drug release modulation [25–27]. More recently, two methacrylate monomers, extensively utilized in dental composites, were polymerized on the surface of pellet cores by means of visible light [28,29]. Photostable functional coatings able to withstand handling stresses were successfully achieved, and an impact on the final release profile was observed as a function of their composition and thickness.

An analogous coating technique, initially exploited in the pharmaceutical field for encapsulation of particles, is the initiated chemical vapor deposition [30]. As the name suggests, gaseous formulations, consisting of vaporized monomers and initiators, are involved. In this case, a thin coating layer is formed when the monomers, along with primary radicals generated by heat activation of the initiator, are adsorbed onto the surface of cooled particles, where polymerization occurs. Depending on the monomers used, differing functional coatings were obtained, including gastroresistant, temperature-responsive and prolonged-release ones [31–35]. Furthermore, the application of a polymeric coating by initiated chemical vapor deposition, synthesized from acrylic precursors directly upon clotrimazole-containing cast films, was recently demonstrated to be a viable approach to prevent crystalline transitions of amorphous compounds [36].

3. Solid-based techniques

3.1 Press coating

Press coating, also referred to as double compression or compression coating, has largely been employed since the first pharmaceutical application was described in the late 50s [37].

This technique entails *(i)* filling of the die of a tableting machine with one half of the overall amount of coating powder formulation, *(ii)* positioning of the tablet core onto the powder bed, *(iii)* filling of the die with the remainder of the powder and *(iv)* final compression to consolidate the applied material into an outer layer of defined thickness.

In order to avoid multi-step processes and circumvent the critical operation of positioning the core inside the die, which may impair the coat thickness homogeneity, a one-step manufacturing method was proposed based on the use of special tableting equipment [38].

The use of double compression necessarily leads to coatings having relatively high thickness, with possible undesired repercussions on the dissolution/release performance, and is limited to cores with appropriate physico-technological characteristics in terms of size, shape and mechanical resistance. Moreover, coating materials with adequate compaction properties can only be applied, and the addition of excipients may be required to improve the outcome of compression.

Although more advantageous techniques, such as spray coating, have been introduced so far, the use of compression coating is still described chiefly for the application of functional polymer coatings intended for modified release [39–42]. In this respect, swellable hydrophilic and microbially degradable polymers have mostly been employed for the purpose of attaining prolonged, pulsatile or colonic oral drug delivery systems. Among swellable hydrophilic polymers, cellulose derivatives, namely HPMC [43–49], HPC [50] and HEC [51], have especially been utilized because of their broad availability at affordable costs and acceptable compaction properties. Although less frequently, the use of PEO has also been reported [52–54]. Coating formulations based on polysaccharides of natural origin, mainly pectin [55–57], guar gum [58,59], xanthan gum [59] and locust bean gum [60] have extensively been employed especially due to their biodegradability by colonic bacteria. The latter two materials were employed in admixture as compression coating agents for the SyncroDose™ chronotherapeutic delivery platform based on the TIMERx® proprietary technology (Penwest Pharmaceuticals Co.) [61,62].

Enteric polymers (Eudragit®S, Eudragit®L and HPMCAS) were also applied by press coating with the aim of attaining pH-dependent systems for colonic release [63–65].

Finally, based on mixed wax and brittle materials as the coating agents, a press-coated delivery platform (Geoclock™) was developed, and a related prednisone-containing product (Lodotra™,

Mundipharma Pharmaceuticals Srl) is commercially available for chronopharmaceutical treatment of early-morning stiffness associated with rheumatoid arthritis [66].
In Table II, the main pharmaceutical applications of press coating and relevant process details are summarized.

3.2 Powder coating

Powder coating techniques involve the deposition of multiple layers of powder, the consolidation of which occurs through particle modifications prompted by heat. Indeed, after initial spreading and adhesion of particles to the substrate, possibly favored by the application of a priming sub-coating of a different material, their heat-induced softening, deformation and coalescence are necessary for a smooth and continuous layer to be formed. Levelling and sintering of the powder layers applied is strictly dependent on the thermo-mechanical behavior of the material at the operating temperature and is aided by the mechanical forces involved. The process has to be carried out above the glassy-rubbery transition temperature (Tg) of the coating formulation so that the particles may undergo plastic deformation. For this reason, plasticizers are often added to lower the Tg of the coating agent, also allowing milder processing conditions to be adopted.
Such techniques generally make use of conventional coating equipment (e.g. fluid bed and rotating pan) provided with devices for the in-line addition of the powder into the processing chamber. The rate of powder feeding can be controlled by single-screw, loss-in-weight or Venturi feeder devices (Figure 3). In all cases, attentive selection of particle size ranges and appropriate flow properties of powder formulations are necessary to ensure reproducibility of the coating thickness.
Powder coating techniques can be classified into thermal adhesion, liquid-assisted and electrostatic processes depending on whether aiding factors are used to promote particle adhesion and, if so, on what factor is concerned (Figure 4).

3.2.1 Thermal adhesion coating

In thermal adhesion coating, elsewhere referred to as heat dry coating, the formation of a coating from layered powders is enabled by heat only [3]. The thermal properties of the coating powder are therefore critical to the outcome of the process.
Plasticizer concentrations up to 40% and thermal post-processing treatments (curing) are generally necessary to enhance the coalescence of particles and allow films of good quality to be formed. Pre-plasticized polymers, obtained by hot-melt extrusion (HME) followed by cryogenic grinding, are generally employed. Talc is normally present in the powder formula to prevent sticking of the units.

The few applications of thermal adhesion described in the literature all rely on the use of acrylic polymers. An existing manufacturing equipment, namely a spheronizer provided with a smooth stainless steel disk, was adapted through the addition of a powder feeding device and an IR lamp positioned on top as a heating source to maintain constant processing temperatures.

In one case, effectively taste-masked and moisture-protected tablets were achieved without plasticizers, thanks to the relatively low Tg of the polymer employed (Eudragit®E PO) [67]. However, an extensive curing phase was required for a continuous and compact film to be obtained, and the inclusion of low-melting excipients in the coating formulation was found to improve powder adhesion.

In another instance, pre-plasticized mixtures of Eudragit®RS and Eudragit®RL, prepared by HME, were applied onto theophylline-containing tablets having a sub-coating of a low melting material [68]. The rate of drug release from the final powder-coated tablets was influenced by the coating level, the plasticizer concentration and the temperature selected for the curing phase.

Finally, Eudragit®L 100-coated tablets containing two different water soluble drugs were also manufactured [69–71]. Formulation variables, such as the nature sub-coating material, the level of plasticizer and the type as well as amount of pore-forming agents, were demonstrated to impact on the mechanical and drug release properties of the coated units.

3.2.2 Liquid-assisted coating

In liquid-assisted dry coating, small amounts of water or aqueous binding solutions are sprayed to help, by interfacial capillary action, adhesion of coating particles to the core surface. In order to completely replace the use of solvents, liquid excipients that are intended to be included in the coating, such as plasticizers, can be employed, which also results in improved particle coalescence. In this respect, a larger amount of plasticizers is generally necessary for film formation in dry- as compared with spray coating techniques.

The adjuvants in the liquid state are added separately from the powder, in a concurrent or alternate mode. Therefore, rotating pans or fluid beds may be provided with a conventional nozzle for spraying of liquids, whereas the coating powder is introduced in admixture with the cores, or by means of powder feeding devices. Otherwise, a three-way nozzle, generally inserted within the core bed, can be adopted to have liquid and powder delivered in close proximity to each other (Figure 5).

A recently proposed alternative to the spraying of plasticizers in the liquid state is represented by their use as powders. These would be spread onto pre-heated core/polymer mixtures inside the coating chamber through two-fluid nozzles based on Venturi effect [72].

In the earliest application of liquid-assisted dry coating, HPMCAS was layered onto pellets and tablets with the aid of a plasticizing mixture consisting of TEC and AMG [73]. The process was performed by different apparatuses, such as a centrifugal granulator, a fluid bed and a ventilated pan coater. After completion of powder feeding, small volumes of water or of an aqueous HPMC solution were sprayed to improve film formation during the curing phase. Although the use of water was not fully avoided, it was possible to reduce the process time to one third as compared with that required by conventional spray coating. By adapting the above-described coating procedure, HPMCAS was also applied to soft gelatin capsules by rotary fluid bed [74]. At first, plasticizers alone were sprayed to prime the capsule surface thus limiting the loss of powder in the early stages of coating. However, due to the adhesive properties of the substrate, HPMCAS needed to be pre-mixed with relatively large amounts of talc in order to overcome sticking of the units.

Silicon dioxide in very limited amounts was investigated as an alternative anti-sticking agent for the coating of pellets with HPMCAS by rotary fluid bed apparatus [75]. Again, TEC and/or AMG were used as plasticizers in the liquid state, and a curing phase was performed [76–79]. An in-depth understanding of the formulation and processing parameters that affect film formation, coating efficiency and storage stability was gained, also by making use of a factorial design of experiments. In other studies, carried out under the same experimental settings, the role of AMG, isopropyl myristate and isopropyl palmitate as capillary force promoters was highlighted. Such compounds proved effective in improving the adhesion of the polymer onto the cores and enhancing the coating efficiency [80,81]. Moreover, liquid adjuvants having good spreading ability, as assessed through contact angle measurements with respect to the coating polymer, were found advantageous for the development of efficient dry coating processes [82].

Recently, liquid-assisted dry coating was exploited to apply HPMCAS onto pellets containing probiotics [83]. Notably, this process allowed higher bacterial survival rates to be attained as compared with conventional coating techniques.

Polymeric materials other than HPMCAS, such as shellac, Eudragit® RS and EC, were also used in dry coating. The latter two materials were employed as coating agents for prolonged-release dosage forms [84–86]. In all cases, emulsions of plasticizers with an aqueous solution of HPMC were sprayed. The release rate from the coated units turned out to be affected by the type and level of plasticizer as well as by the curing conditions, whereas the physical stability of the product was improved by the use of micronized coating powders.

In another instance, pre-plasticized EC was used as the coating polymer. Pre-plasticization was obtained by HME co-processing or adding the plasticizer(s) to commercially available aqueous

polymer dispersions (Aquacoat®, Surelease®), which were then spray-dried to yield powders suitable for dry coating [87].

3.2.3 Electrostatic coating

Coating procedures based on electrostatic charging of powders are well-established in the metal-finishing industry and are now of interest also for the development of drug dosage forms and medical devices [3].

In pharmaceutical coating, electrostatic forces are exploited to promote the adhesion of powder particles to the substrates, mainly tablets or pellets. The process is generally carried out by grounded rotating pans provided with an electrostatic gun, through which the coating particles are charged via differing mechanisms and sprayed onto the cores [88]. After deposition, the powder has to remain in place long enough to enable film formation by heat-induced coalescence of the individual particles. A smooth and homogeneously thick coating is achieved by reduction of the free volume, while its hardening takes place on cooling [89]. Any powder able to accumulate charge with a low decay rate is potentially suitable for being employed as an electrostatic dry coating agent [90].

Because many materials of pharmaceutical interest can retain electric charges, powder charging has been used not only for coating but also in other manufacturing operations. For example, it was exploited to improve the active pharmaceutical ingredient (API) content uniformity in mixing, and to obtain thin films by solvent-free deposition of API/polymer blends [91–93].

Electrostatic charging of particles may be obtained via a triboelectric or corona mechanism. In tribocharging, charge accumulation results from friction between the fluidized coating particles and the wall of a triboelectric gun, according to the well-known phenomenon of electron transfer that occurs when different materials are rubbed with each other and then separated. The same mechanism is operating when charges are generated during powder handling in several pharmaceutical processes. The gun wall is generally made of polytetrafluoroethylene that tends to assume negative charges, thereby leading to positively charged particles. Tribocharging is rather a complex and poorly predictable operation because it is markedly influenced by many factors, such as particle properties (electrical resistivity and surface roughness) and environmental conditions (temperature, relative humidity) [90,94,95]. For this reason, triboelectric charging is less commonly effected than corona charging.

Corona charging, also referred to as corona discharge, entails that particles accumulate charges onto their surface by crossing an electric field in the presence of free ions. Corona gun devices include an electrode able to generate a potential gradient with a neutral or grounded substrate when a high

voltage is applied. This allows free ions to be obtained by stripping electrons from gas molecules surrounding the electrode. Therefore, the coating particles, sprayed by the gun in the direction of the substrates to be coated, are introduced into the electric field that has established in the area between the emitting electrode and the grounded surface. According to the field charging mechanism, the perturbation of the field provoked by the particles results in free ion deviation and adsorption.

A major drawback of corona charging is the possible accumulation of charges on the surface of the substrate, which would prevent adhesion of further coating particles. Moreover, the oppositely charged ions that are formed may neutralize the incoming charged particles and, also, those already deposited, possibly causing their ejection from the coating layer and consequent defects in its surface.

In electrostatic coating, it is often necessary to enhance the conductivity of the core dosage forms. In this respect, a short-lasting exposure of the substrate to high humidity conditions was proposed with the aim of having water molecules adsorbed prior to powder deposition [96]. More recently, the spraying of small amounts of plasticizers in the liquid state was alternatively undertaken. Thus, not only the electrostatic deposition of particles was enhanced, but also their adhesion and coalescence could be improved, by capillary action and Tg reduction, respectively. The combined use of liquids and electrostatic charging was successfully applied to the coating of tablets and pellets with different polymers, intended for immediate, prolonged or enteric release [97–101].

In particular, the coating efficiency was found higher when employing both electrostatic charging and plasticizers in the liquid state as compared with the sole plasticizers. Moreover, it turned out to be influenced by the charging voltage of the electrostatic gun [99,100].

An example of industrial application of electrostatic dry powder coating is represented by LeQtracoat® technology (Diurnal Group PLC), developed by Phoqus Pharmaceuticals [102]. In a custom-designed equipment, the coating of tablets takes place according to the same principle used in photocopying for the deposition of ink toner. The coating material is applied to one side first and then to the other. The extent of precision allowed is such that images (brands, signs) can be imprinted on the tablet surface. By LeQtracoat® technology, clinical batches of Chronocort®, a modified-release formulation of hydrocortisone for the treatment of adrenal hyperplasia, were manufactured [103,104].

In Tables III-V, the main pharmaceutical applications of powder coating techniques, namely thermal adhesion, liquid-assisted and electrostatic coating, respectively, are summarized along with the relevant process details.

4. Other techniques

Different techniques based on hot processing of thermoplastic polymers, widely exploited in many industrial areas albeit only marginally in the pharmaceutical field, are deemed to fall within the scope of this review article in that they allow coated-like dosage forms to be manufactured without the use of solvents. Such dosage forms may be presented in the form of core+shell systems or of capsular devices consisting in functional shells filled with drug formulations.

Injection molding (IM) and three-dimensional (3D) printing by fused deposition modeling (FDM) are the main solventless techniques employed for fabrication of coated-like dosage forms. While IM holds great potential with respect to its possible suitability for continuous manufacturing, FDM 3D printing is especially attractive as a real-time prototyping technique and as a tool for medicine personalization.

In IM, a properly softened or melted material is injected, under high pressure conditions, into a 3D mold, by which it is shaped into the finished item on cooling [105]. IM represents a versatile manufacturing technique in that it enables the production of objects with different size and shape as well as detailed geometries. Over the last years, it has drawn much attention due to its viable exploitation in either the manufacturing of consolidated dosage forms or the development of original delivery systems with peculiar design and enhanced therapeutic performance.

A capsular device obtained by IM was proposed for extended residence within specific regions of the gastrointestinal tract [106]. For this purpose, a small magnet was inserted into the capsule, which could be kept at the target site by positioning an external control magnet in the corresponding area of the body surface. Such a device was manufactured starting from polymers that were demonstrated to be biodegradable to a different extent.

Egalet® is a delivery platform produced by IM and developed for either prolonged or pulsatile release [107]. In the prolonged-release configuration, it consists in a drug-containing hydrophilic erodible matrix enclosed within a shell provided with two openings at each end, composed of an insoluble and impermeable polymer. The rate of drug release from the inner matrix is controlled through a diffusion/erosion-based mechanism. Because only the two bases of the matrix come into contact with the gastrointestinal fluids, zero-order kinetics can be achieved, which is exploited for reducing the daily frequency of drug dosing, particularly with opioids in pain management. In this instance, the formulation is specifically conceived to resist physical and chemical manipulation methods, thus lowering the risk of misuse and addiction (Egalet Guardian™ Technology) [108]. The Egalet® system in its pulsatile-release configuration was attained by positioning, at the open

ends of the shell, two erodible polymer plugs able to impart a delay phase through their surface erosion. The core and shell components of these devices were basically fabricated by one-step IM processes involving two successive injections from distinct nozzles into a single mold, wherein cavities to be filled with the concerned materials were timely created by the alternate movement of a plunger.

The Chronocap® delivery platform consists in a functional capsular container formed from a cap and a body, able to convey differing drug formulations [109]. The release of the active molecule can be modulated by selecting the appropriate composition (type of polymer, presence of other excipients) and design characteristics (geometry, wall thickness) for the shell. Capsular devices based on swellable/erodible (HPC) or enteric-soluble (HPMCAS) polymers were obtained by IM after design of special molds [110,111]. The HPC shells, filled with a model drug, were shown to give rise to pulsatile release, lag time being related to their thickness. Such a system was proposed for time-dependent colon delivery following application of a gastroresistant outer film by spray coating [112].

As any 3D printing process, FDM is an additive manufacturing approach that involves the deposition of successive layers of material to construct objects from their digital models. In this technique, the printer is fed with filaments produced by HME, and the thermoplastic material, properly melted/softened, is applied by a heated extrusion head moving along the x and y axes above a build plate that moves along the z axis. The item under construction thus grows in the bottom-up direction [113].

The Chronocap® system for pulsatile release was also fabricated by FDM, showing comparable performance *versus* a reference formulation produced by IM [114]. This finding pointed out the potential advantages such a technique may offer not only as a manufacturing strategy for personalized drug delivery but also as a rapid prototyping tool for the molded capsular device.

Finally, by means of a dual 3D printer, suitable for concurrent deposition of different materials, a gastroresistant tablet was recently produced [115]. The enteric-soluble shell and the drug-containing core, made of Eudragit®L 100 and PVP, respectively, were shaped within a single-step process.

5. Conclusions

In the pharmaceutical field, dry coating techniques are proposed with the aim of avoiding or limiting the drawbacks associated with the use of solvents. Although spray coating definitely remains the most popular approach to attaining coated dosage forms, the need for processes suitable

for water-sensitive drugs or formulations, together with an increasing demand for less costly production, has been prompting the research in this area of pharmaceutical technology.

Among the diverse processes discussed in this overview, traditional and well-established press coating, exploited for the manufacturing of a number of commercially available products developed in the past, is currently proposed for fabrication of oral delivery systems mainly intended for pulsatile, colonic or prolonged release when other techniques are not viable.

Besides press coating, which involves utilization of conventional or customized tableting machines, other techniques, particularly melt coating and powder coating, rely on already available equipment following proper adaptation to the specific operating modes and conditions. Such techniques may thus have concrete chances of industrial application, provided that appropriate large-scale facilities can be developed. On the other hand, in the case of less consolidated processes, such as photocuring and initiated chemical vapor deposition, more difficulties are likely to be encountered not only because of the technical issues related to the construction of purposely devised apparatuses, but also due to the safety constraints and consequent regulatory burden to be faced.

More recently, on account of the growing popularity of hot-processing techniques, innovative approaches intended for attainment of coated-like dosage forms, based on IM or FDM 3D printing, have increasingly been investigated as an alternative to standard coating procedures and are being looked at as a topic of great interest for the future of pharmaceutical manufacturing.

Disclosure of interest

The authors report no conflicts of interest.

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FIGURE CAPTIONS

Figure 1: classification of solventless techniques used to obtain coated or coated-like dosage forms.

Figure 2: nozzle for hot-melt coating having triaxial structure without (left) and with (right) Teflon insulation: entries for *a)* melted coating material, *b)* nebulizing air flow, *c)* heated compressed air (Adapted from [9]).

Figure 3: rotating pan equipped with a powder-feeding device (Courtesy of IMA S.p.A., Italy).

Figure 4: outline of dry powder coating techniques.

Figure 5: three-way nozzle (left) and rotor insert of a fluid bed (GPCG 1.1, Glatt®, Germany) with the nozzle in place (right).

Figure 6: cross section of a press-coated tablet.