Advances in solid dosage form manufacturing technology

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Currently, the pharmaceutical and healthcare industries are moving through a period of unparalleled change. Major multinational pharmaceutical companies are restructuring, consolidating, merging and more importantly critically assessing their competitiveness to ensure constant growth in an ever-more demanding market where the cost of developing novel products is continuously increasing. The pharmaceutical manufacturing processes currently in existence for the production of solid oral dosage forms are associated with significant disadvantages and in many instances provide many processing problems. Therefore, it is well accepted that there is an increasing need for alternative processes to dramatically improve powder processing, and more importantly to ensure that acceptable, reproducible solid dosage forms can be manufactured. Consequently, pharmaceutical companies are beginning to invest in innovative processes capable of producing solid dosage forms that better meet the needs of the patient while providing efficient manufacturing operations. This article discusses two emerging solid dosage form manufacturing technologies, namely hot-melt extrusion and fluidized hot-melt granulation.

Keywords: hot-melt extrusion; melt granulation; drug delivery

1. Introduction

Oral dosage forms such as tablets and capsules are considered the most patient-acceptable dosage forms available today. Not only do they offer convenience and ease of handling, but also they are extremely stable (chemical and physical), have a high throughput and are relatively inexpensive to produce. Orally administered dosage forms are an intricate blend of pharmaceutical excipients and active pharmaceutical ingredients (APIs) that must be adequately mixed and/or granulated to ensure the manufacture of acceptable pharmaceutical products. Pharmaceutical granulation is often necessary to overcome the significant compression difficulties and erratic flow properties of many APIs; characteristics that often limit the successful production of acceptable dosage forms (Kaerger et al. 2004). Although pharmaceutical granulation is often necessary, it is a batch process that provides a bottleneck for the implementation of continuous manufacturing for orally administered solid dosage forms. While the pharmaceutical industry has historically used batch and not continuous

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processes, the significant decrease in profit margins and the need to maintain high competitiveness and constant growth has driven pharmaceutical companies to invest in new and innovative processes that better meet the needs of the patient while providing efficient manufacturing operations (Vervaet & Remon 2005). In summary, this article will provide an overview of two key technologies (hot-melt extrusion (HME) and fluidized hot-melt granulation (FHMG)) that are emerging within pharmaceutical technology.

2. Current solid dosage form manufacturing technology

Orally administered solid dosage forms are a blend of pharmaceutical excipients, such as diluents, binders, disintegrants, glidants, lubricants and APIs. The successful manufacture of pharmaceutically acceptable products is dependent upon the ability to adequately mix and/or granulate these materials to ensure that the resultant solid agglomerates possess high fluidity, compressibility and in addition avoid de-mixing during post-granulation processes, most notably during compression (tablets) or filling (capsules). Moreover, the final characteristics of the dosage form such as drug dissolution, disintegration, porosity, friability and hardness are all significantly influenced by the properties of the powder blends used during their manufacture (Lieberman & Lachman 1981). During product manufacture, large volumes of powder are fed through production equipment/processes and it is essential to be able to accurately determine, define and control powder properties to ensure reproducible manufacture and consistent product performance. The agglomeration processes most typically used to ensure powder blends possess adequate fluidity, cohesiveness and compressibility involve either wet or dry methods.

Wet granulation, encompassing low- and high-shear mixing, fluid-bed mixing (spraying) and wet-mass extrusion, is an extremely versatile technique that has several advantages over dry methods, including improved control of drug content, better uniformity for highly potent drugs (low-dose APIs) and production of granules with superior bulk density and compatibility (high- and low-dose APIs). Wet granulation typically involves wet massing a blend of API and excipients in a wet granulator followed by subsequent sieving and finally drying (Aulton 2002). The most commonly used liquid for wet granulation is water although non-aqueous solvents such as ethanol and isopropyl alcohol may be used when water is unsuitable. While water is extremely economical and environmentally friendly, wet-granulation techniques are labour intensive and process times are inherently long due to wetting and drying stages (Kristensen & Schaefer 1987). Such disadvantages may be overcome through the use of volatile non-aqueous binder solutions, but these typically require specialized equipment due to the high flammability of the solvent. Moreover, during wet-granulation processing (milling, wet massing, drying and compression), phase transformations may be induced including changes in polymorphic form, state of solvation and degree of crystallinity of the API (Hendriksen et al. 1995). These phase transitions are known to significantly influence the physicochemical properties of solid materials and, in particular, API activity (Yoshika et al. 1995). An example of the importance of such phase transitions during wet granulation has recently been reported by Wardrop et al. (2005). Abbott-232, a
highly water-soluble, non-hygroscopic, potent uroselective $\alpha_{1A}$ agonist, has been shown to undergo a solution-mediated phase transformation from an anhydrate to an amorphous form during wet granulation, which subsequently decreased the potency of the API. Interestingly, the anhydrate would not reform from the monohydrate (formed during wet granulation) during the drying stages of the process due to the presence of crystallization inhibitors within the formulation. Typical examples of crystallization inhibitors include polyvinylpyrrolidone (PVP), hydropropyl methylcellulose (HPMC) and other high-molecular-weight polymers that significantly increase the viscosity of the system and prevent formation of a crystal lattice.

More recently, Tantry et al. (2007) demonstrated that the physical form of theophylline manufactured in a solid dosage form is significantly influenced by the molecular weight of the binding agent, the granulation method and the drying temperature. In this study, a stable anhydrous form of theophylline was manufactured into tablets using a high-shear wet (aqueous-based) granulation process. During the granulation process, theophylline monohydrate was formed that was partially converted to a metastable anhydrous form during drying. Storage of these dosage forms at RH > 33% caused complete metastable anhydrous to stable anhydrous conversion accompanied by a pronounced decrease in the initial dissolution rate. The presence of PVP decreased the conversion of the metastable anhydrous to stable anhydrous theophylline, with high-molecular-weight PVP being more effective. Furthermore, increasing the drying temperature from 45 to 55°C significantly increased the metastable anhydrous to stable anhydrous conversion.

Although the presence of pharmaceutical excipients may significantly alter the rate and/or extent of phase transformation and recrystallization during the wetting and drying stages of wet granulation, it has been shown that their inclusion may significantly decrease product storage stability. Hydrochlorothiazide, a drug substance with excellent solid-state stability, can undergo hydrolysis to form formaldehyde and 4-amino-6-chloro-1,3-benzenedisulphonamide. Desai et al. (1996) have shown that the inclusion of povidone K-30 NF (PVP) as a binder and poloxamer 188 NF (Pluronic F68) as a wetting agent significantly increases drug hydrolysis during storage. Replacement of PVP with Starch 1500 and removal of Pluronic F68 from the tablet formulation resulted in lower levels of degradation. The increased drug degradation in the presence of PVP and/or Pluronic F68 was attributed to the enhanced solubility of the drug, in the moisture present in the tablets. While non-aqueous solvents may be employed to prevent aqueous-induced transitions and/or hydrolysis, phase transformation may still occur during processing. Moreover, the use of non-aqueous granulating fluids may also lead to a significant change in granule characteristics, such as fracture strength, bulk density and compactability (Fichtner et al. 2007). It is well accepted, therefore, that it is not only the properties of the API and the excipients that significantly influence the final characteristics of the product but also the conditions (amount/type of granulating liquid, granulation time, airflow rates and drying temperature/rate) of the wet-granulation method.

Dry methods are a suitable alternative to wet granulation particularly when the API or excipients are sensitive to water/moisture and non-ambient temperatures, conditions that are typical for wet granulation. Dry granulation typically involves the compaction of powder blends through slugging or roller
compaction. Slugging involves the manufacture of a large compressed tablet whereas roller compaction pushes powder blends through two counter-rotating rolls, producing a sheet of agglomerated material. In both cases, the formed solid compact is milled to produce the granulate of the desired particle size range for compression or filling. Given that dry granulation does not involve the use of solvents, solution-mediated phase transformations are negated; however, dry granulation may introduce the possibility of phase transformation during the application of high-compression forces and localized heating while agglomerating powder blends (Zhang et al. 2004). APIs known to undergo phase transition upon exposure to mechanical stress are discussed in a mini-review by Brittain (2002). Typical examples of APIs that undergo transformation during compression include caffeine and chlorpropamide. Interestingly, dry granulation processes produce granules with an extremely high bulk density and low intragranular porosity in comparison with granules produced using alternative techniques (Li & Peck 1990). Furthermore, dry-granulated materials exhibit better gravimetric flowability; however, the high-density granules produced using this process have been shown to suffer from loss of tabletability, due to the significant number of particle defects and loss of plasticity introduced during processing (Malkowska & Khan 1983). This is extremely important, as the quality of the final dosage form is significantly influenced by the compaction properties of the granular material (Joiris et al. 1998). In addition to loss of tabletability and possible phase transformation during compression, dry granulation may also result in high levels of dust (problematic for potent API), poor compaction homogeneity and high levels of adhesion to the production equipment. Consequently, while dry granulation is conceptually very simple with low operational costs, a considerable lack of process understanding limits its use (Gereg & Cappola 2002). These disadvantages combined with a willingness to accept static agglomeration processes have led to wet granulation remaining the preferred and most widely accepted method for size enlargement within the pharmaceutical industry. More recently, however, oral dosage form manufacturing technology is enjoying a significant renaissance, with a number of key emerging technologies that may offer a suitable alternative to currently available processes and more importantly negate the current drawbacks associated with processing pharmaceutical powders and solid dosage forms.

3. HME and FHMG: emerging technologies

HME and FHMG are two highly dynamic topics with the potential to radically change the way in which oral dosage forms and drug delivery platforms are manufactured. FHMG is a non-ambient temperature process that uses meltable binders to agglomerate fluidized dry powders whereas HME involves the use of thermoplastic polymers for the production of controlled drug delivery systems. Both processes may be used to manufacture granules, pellets and tablets and in particular HME may be used to produce highly innovative multiple medications. Moreover, such processes may be used to produce thermodynaramically stable solid solutions to improve the dissolution rate of poorly water-soluble drugs, one of the major challenges in dosage form development (Chokshi et al. 2005). Unlike conventional solid dosage form manufacturing techniques, both processes
avoid the problems associated with drug instability, flammable solvents and time-consuming drying processes, ultimately reducing the time required for product manufacture (Walker et al. 2007a,b). Additionally, there is a significant reduction in the number of processing steps, no prerequisite compression/fluidity properties are required and improved drug/polymer mixing and hence drug distribution and product homogeneity may be observed (McGinity 2004).

4. Hot-melt extrusion

HME is an innovative drug delivery technology that is receiving increased attention from both the pharmaceutical industry and the academic community. HME was first developed in the plastics industry and in its most basic form, compacts, blends and converts a powder mix into a product of uniform density and shape (Crawford 1998). At the most fundamental level, a single screw extruder consists of one rotating screw positioned inside a stationary barrel (figure 1), whereas more advanced machines involve twin-screw systems using either a co-rotating or counter-rotating screw configuration. As shown in figure 1, the barrel of an HME machine consists of three distinct zones: feed zone; compression zone; and a metering zone, all of which exert a different pressure on the pharmaceutical powder. These three zones differ in the depth and/or pitch of the screw flights. The feed zone has an extremely large screw flight depth and pitch (figure 2), allowing for consistent feeding from the hopper and gentle mixing of the API and excipients. At this stage of the process, the pressure within the extruder is at its lowest. The subsequent compression zone imparts a high degree of mixing and compression to the material by decreasing the screw

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pitch and/or the flight depth, which results in a gradual increase in pressure along the length of the compression zone (Breitenbach 2002). The primary function of this zone is to melt, homogenize and compress the extrudate so that it reaches the metering zone in a form suitable for extrusion. The function of the metering zone is to ensure that the extrudate has a uniform thickness, a property that is governed by the consistency of melt flow. Consequently, the metering zone must eliminate any pulsating flow and the constant screw flight depth and pitch reflect this aim. While the screw pitch and flight depth are constant, the pressure in this zone far exceeds the pressure in the feed zone. The application of this continuous high pressure ensures a uniform delivery rate of molten material through the extrusion die and hence a uniform product. Given that HME is a non-ambient process involving the use of thermoplastic polymers, heat is commonly transferred to the powder mass through a combination of friction (rotation of screw in barrel) and barrel heaters.

HME technology offers several distinct advantages over manufacturing techniques that have been typically used to produce orally administered solid dosage forms. The technique does not involve a granulation fluid and thus avoids problems associated with instability (McGinity 2004). Moreover, extruded materials may be cut directly into tablets or pellets avoiding subsequent compaction processes, typically required for wet- and dry-granulation techniques. Therefore, HME allows for the rapid production of solid dosage forms while avoiding many of the current disadvantages of conventional manufacturing techniques. HME is a non-ambient process that involves the use of thermoplastic polymeric materials as carrier systems for the API. Although thermoplastic materials such as polyethylene (PE) and polypropylene are well accepted within the plastics industry, such materials are not suitable for the manufacture of orally administered solid dosage forms. Consequently, only when pharmaceutically approved polymeric materials (PVP, polyethylene oxide (PEO), Eudragit and PE glycol (PEG)) became widely available did HME emerge as a suitable drug delivery technology. While residence time within the extruder and high processing temperatures (required to melt the polymeric carrier) were initially projected as significant disadvantages of this technology, the use of plasticizing agents and the introduction of twin-screw extruders negated such concerns. Typical plasticizing agents for HME include PEGs (Zhang & McGinity 1999), triacetin (Follonier et al. 1994) and citrate esters (Aikten-Nichol et al. 1996). However, APIs have also been shown to be effective plasticizers in many cases (Repka & McGinity 2000). These agents (plasticizers) occupy sites along the polymer chain and prevent chain–chain interactions significantly reducing the frictional forces between chains, thus improving polymer chain mobility and processability (Doolittle 1954).

Initial investigations in this area focused on the effects of plasticizing agents, processing conditions and API loading on the physicochemical properties of the extruded dosage forms. Zhang & McGinity (1999) reported the influence of polymer molecular weight, API loading and the inclusion of PEG on the dissolution of chlorpheniramine from PEO matrix tablets. Drug release from the matrix was controlled by PEO erosion and by the diffusion of the API through a swollen gel layer that developed at the surface of the tablets during dissolution experiments. In a further study, Crowley et al. (2002) investigated the thermal stability of PEO, illustrating that lower-molecular-weight PEO was more
susceptible to degradation, and vitamin E and vitamin E tocopheryl succinate PEG 1000 (TPGS) were found to be highly suitable stabilizing agents. An investigation by Liu et al. (2001) examined the properties of wax-based HME tablets and granules and compared them with tablets/granules prepared using a high-shear melt granulation (MG) method. MG is a non-ambient single-step high-shear granulation method in which powder agglomeration is promoted by the addition of a low-melting-point binder (Fichtner et al. 2007). Similar to HME, MG is a useful alternative to conventional wet-granulation processes when the use of solvents is not possible (Schaefer et al. 1990). The study by Liu et al. (2001) illustrated the potential use of low-melting (50–60°C processing temperatures) wax materials and matrix carriers. Interestingly, tablets prepared using HME were much harder and released the API (phenylpropanolamine) much more slowly than comparator tablets prepared using high-shear MG. Moreover, the uniformity of API within HME granules was much better than those prepared using high-shear MG and hence drug dissolution was more consistent.

While preliminary studies have focused on the effects of formulation and processing variables on the properties of the dosage form, subsequent scientific articles have described the use of HME for the production of solid solutions and for the development of mini-matrices. Early work by De Brabander et al. described the use of HME to prepare matrix mini tablets that provide less risk of dose dumping, less inter- and intrasubject variability and high levels of dispersion within the digestive tract (De Brabander et al. 2000). Further investigations by De Brabander et al. (2003) studied the manufacture of sustained release multiple unit dosage forms (mini-matrices) using ethyl cellulose, HPMC and ibuprofen. In relation to the preparation of drug delivery systems with improved aqueous solubility, HME provides a suitable platform for the preparation of solid solutions provided there is a high degree of miscibility between the API and the polymeric carrier (Leuner & Dressman 2000). Mehuys et al. (2004) described the use of HME for the production of a matrix-in-cylinder device for sustained release purposes. This system resulted in a fourfold increase in the bioavailability of propranolol when compared with a commercially available formulation (Inderal). The use of HME to produce solid solutions to improve the dissolution properties of active agents has long been recognized. Owing to the non-ambient nature of the process, HME provides an efficient technology for the dispersion and solubilization of APIs within a thermoplastic matrix. Given that improving the solubility, dissolution rate and, thus, in vivo absorption properties of new drug candidates remains a major challenge in the development of new drug treatments, the emergence of a novel technology that is capable of producing solid solutions while negating common manufacturing disadvantages is highly beneficial. One major concern regarding the formation of solid solutions via this technique is the phase transition (recrystallization) that may occur upon storage leading to a significant reduction in the aqueous solubility and unpredictable product performance.

Early research by Hulsmann et al. (2000) investigated the use of PEG, PVP and gelucire HME extrudates to improve the solubility of 17β-oestradiol. HME extrudates significantly improved the solubility of this API with a reported 30-fold increase in dissolution rate. More recently, Six et al. (2005) investigated the performance of itraconazole solid dispersions prepared by HME and
compared the clinical performance of the extrudates to a marketed form, Sporanox. A further study by Verreck et al. (2005) examined the use of supercritical carbon dioxide (scCO2) as a temporary plasticizer during the manufacture of solid dispersions of itraconazole and polyvinylpyrrolidone-co-vinyl acetate 64 (PVP-VA 64). Given that the stability of a solid dispersion/solution is governed by matrix mobility, temporary plasticization may provide a suitable method of avoiding post-manufacture recrystallization. A significant reduction in the processing temperatures was achieved using scCO2 without any detrimental effects on the extrudates. Interestingly, the macroscopic morphology was significantly altered due to expansion of the scCO2 at the die, resulting in foamed extrudate, increasing surface area, porosity and hygroscopicity. Furthermore, milling efficiency was improved. Although considerable research has been conducted using PEO as a drug carrier in HME, Li et al. (2006) recently reported the use of PEO as a matrix carrier for improving the solubility of a model, poorly water-soluble API (nifedipine). Hot-stage microscopy illustrated that nifedipine could form miscible dispersions at temperatures above 120°C with complete loss of nifedipine crystallinity and a significant improvement in dissolution rate compared with either pure nifedipine or a physical mixture of PEO and nifedipine. In another study, the formation of PEO/clotrimazole solid solutions using HME was reported by Prodduturi et al. (2005). Interestingly, the solid solution was shown to be unstable and recrystallized after three months storage at 25°C and 60% RH. The authors proposed that the instability of the formulation was due to folding (occurred during HME) and unfolding (occurred during storage) of linear PEO chains. Similarly, PVP was the focus of many early investigations into the feasibility of HME but more recently it is enjoying a renaissance, particularly for the preparation of solid solutions. Patterson et al. (2007) have recently reported the use of PVP in the formation of glass solutions using carbamazepine, dipyridamole and indomethacin. HME materials exhibited improved solubility in comparison with those prepared by spray drying, and it was shown that the stability of solid solutions may be greatly enhanced by the formation of hydrogen bonding between the parent polymer and the API.

Undoubtedly, due to the inherent advantages associated with HME, there is growing interest in this technology for the production of immediate and sustained release delivery systems, whether they are in the form of tablets, granules, pellets or films. Research to date has examined the formation of many types of orally administered dosage forms and has identified the limitations as well as the significant benefits this technology may afford. Interestingly, as this technology begins to gain momentum, the number of research articles being published has dramatically increased. In order for HME to fulfil its true potential new research must address the major challenges facing oral dosage form development. Improving the solubility, dissolution rate and, thus, in vivo absorption properties of new drug candidates remains a major challenge in the development of new drug treatments. Hence, there is continuing interest in the development of new processing technologies, and in particular, HME, to enhance the dissolution of poorly water-soluble drugs. Recently published articles on HME have focused on improving drug solubility through the formation of solid solutions; however, understanding API stability in the dosage form remains a major challenge. This coupled with the need to advance the simplistic nature of
single-matrix systems to manufacture multi-functional dosage forms must be addressed so that HME can open new scientific horizons and go substantially beyond the current state of the art.

5. Fluidized hot-melt granulation

Granulation is often used within the pharmaceutical industry to increase the average particle size within a powder blend so as to make the blend more amenable to subsequent compaction processes and hence improve the overall reproducibility of solid dosage form manufacture. Granulated material may typically provide less segregation of the constituents of the powder, improve flowability and very importantly improve powder compactability, leading to a highly uniform, acceptable product. It is common for APIs and other excipients to be mixed, granulated, sieved and dried prior to tableting: processes that are pertinent to the successful manufacture of acceptable dosage forms but are very time consuming. Although pharmaceutical granulation is an extremely laborious process, it is an extremely important unit operation given that the properties of the resultant granules may significantly influence the dissolution rate, disintegration time, friability and hardness of the final solid dosage form. Moreover, the physicochemical properties of granules will ultimately influence their processability, fluidity and compressibility (Sun & Grant 2001). Conventional granulation processes are employed within the pharmaceutical industry to agglomerate powders to produce granules of the desired shape and size; factors that are pertinent to overall tabletability (Laitinen et al. 2004). Currently used methods are associated with significant disadvantages including long process times, potential loss of API activity, poor compressibility, uneven and erratic flow through manufacturing hoppers and high development costs. Consequently, it is well accepted that a novel process negating such difficulties would be highly superior and dramatically improve powder processability ensuring the reproducible production of elegant solid dosage forms with high patient acceptability.

One such emerging technique is FHMG. Fluidized beds have several applications within the processing of orally administered solid dosage forms, most notably during drying and granulation. For the purposes of granulation, the majority of research conducted in this area has focused on the use of binding fluids that are sprayed onto fluidized particles. FHMG differs significantly in that it is a non-ambient process conducted at elevated temperatures to change the physical nature of one or more of the components. Thus, FHMG involves the use of meltable binders to agglomerate fluidized dry powders (Walker et al. 2006). FHMG avoids the use of solvents negating the problems associated with in-process hydrolysis and solvent removal. Furthermore, it does not require powders to possess high levels of fluidity and compressibility. Conventional wet techniques typically involve transfer of powder mass which may involve losses in transfer, contamination of manufacturing equipment, increased processing and operator time and increased dust levels (issues that are particularly pertinent when manufacturing dosage forms containing highly potent drugs). In contrast, FHMG appears to be a simple, rapid and safe process with significant advantages.
The earliest work reported was conducted by Kojima & Nakagami (2001) and investigated the use of FHMG as a means of granulating micronized low-substituted hydroxypropyl cellulose (LH41). Although LH41 is extremely favourable as a controlled release matrix carrier, the poor flowability and compressibility of this material has limited its use in standard tableting processes. Interestingly, FHMG was shown to preserve the controlled release properties of LH41 while improving the flowability, hence improving subsequent tablet manufacture. As with all novel processes most fundamental, early investigations focus on investigating variables that significantly influence granule properties including process and formulation variables (Kristensen & Schaefer 1987). In this respect, Kidokoro et al. (2002) investigated the use of FHMG as a novel granulation process using PEG and glyceryl monostearate as meltable binders. One of the most interesting aspects of these early investigations was that tablet hardness and disintegration were not affected by tablet porosity highlighting that tablets with high reproducibility may be processed under a wide range of compression forces. Another interesting article by Kidokoro et al. (2003) investigated the effect of the crystallization behaviour of PEG 6000 on the properties of granules prepared by FHMG. The authors demonstrated that the particle size distribution of the resultant granules was significantly influenced by the crystallization behaviour of the meltable binder. While early studies on FHMG were extremely promising and highlighted the significant potential for the preparation of pharmaceutical granules, the detailed mechanism of granule growth and the relationship between the growth parameters and the properties of the granules that will ultimately determine the performance of the product were poorly understood. As with any new process, identification of the relationships that exist between granule characteristics, process parameters and formulation variables must be established (Fung & Ng 2003). One of the first investigations to examine granule growth mechanisms was conducted by Seo et al. (2002). The effect of binder droplet size and type of binder on granule growth mechanisms within the fluid bed was investigated. Initial granule growth was shown to occur via nucleation of filler particles (in this case lactose) in the molten binder droplets whereas increased massing occurred due to coalescence between agglomerates. Interestingly, at high process temperatures, binder droplet size and binder type had no significant effect on the average granule size at the end of the process. The kinetics of breakage within the fluid bed during MG has been examined by Tan et al. (2004). In this study, mathematical models were developed and verified using population balance modelling (PBE). Additionally, a new analytical PBE and discretized population balance equation were developed for the growth and nucleation process. A further investigation by Tan et al. (2005) quantified the aggregation and breakage rates within the fluidized bed during the MG process. Granulation rate was observed to increase with increased bed temperature using a high-viscosity binder but granulation rate reached a plateau for less viscous binders. Furthermore, granulation rate also increased when binders of a larger droplet size and lower fluidizing velocity were employed. The overall kinetics during the process has been identified to be a combination of particle aggregation, binder solidification and granule breakage (Tan et al. 2006). Granule growth was shown to be directly dependent upon the amount of binder used and binder particle size. Moreover, increased fluidization velocity was shown to reduce granule growth rate.

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One of the first studies conducted by our group investigated the MG of lactose and PEG using a fluidized bed granulator (Walker et al. 2006). Rather than spraying molten binder onto the fluidized particles, all the components including the binder were introduced to the fluid bed in the solid state. The effect of process parameters such as binder content and binder viscosity was correlated to granulation time and particle size distribution. The experimental data indicated that after initial nucleation the granulation mechanism was dependent upon binder content and binder viscosity. When the binder content was increased de-fluidization of the bed occurred and granulation moved to the slurry regime. Granulation with relatively low-viscosity binders resulted in granule growth by coalescence; however, an increase in binder viscosity resulted in less coalescence and a lower granule growth rate. More recently, FHMG has been used for the agglomeration of model pharmaceutical powders (Walker et al. 2007a, b) and a meltable model API (ibuprofen). In this investigation, ibuprofen was used as the binder. Using a novel high-temperature method, the compression properties of the granules were measured. It was found that the fractural modulus of the granules at non-ambient conditions was orders of magnitude lower than that measured under ambient conditions. Interestingly, after an initial period of nucleation only velocities within the high-shear region of the fluidized bed were sufficient to promote granule deformation and, therefore, coalescence. Furthermore, dissipation of the viscous molten binder to the surface of the agglomerate was the most important factor in the latter stages of the granulation process. From a pharmaceutical perspective, the inclusion of ibuprofen with PVP in the co-melt process proved to be highly significant. It was found that there was a significant decrease in the heat of fusion associated with the melting of ibuprofen within the FHMG systems, suggesting loss of crystallinity.

In addition to characterizing the effect of process and formulation parameters on the final properties of the granules, we have investigated the use of Raman spectroscopy for characterizing the granulation process within the fluid bed. In situ measurement of bed composition within the fluidized bed (three spatial dimensions) as a function of time has been investigated using Raman spectroscopy (Walker et al. 2007a, b). Raman spectra were recorded from specific volumes of space and used to provide three-dimensional maps of the concentration and chemical structure of the particles in a fluidized bed within a relatively short time window. At the most basic level, the technique measures particle density via the intensity of the Raman spectra. More importantly, the data also provide information on the chemical structure of the fluidized particles.

FHMG has significant potential as a novel granulation process and is gaining increased academic attention. This process does not involve the use of extraneous binding fluids that may decrease API stability and produce significant phase transformations during processing. Furthermore, hydrophobic (stearic acid or triglycerides) and hydrophilic materials (PEG or poloxamer) may be used to enhance the dissolution rate of poorly soluble drugs, thereby yielding the possibility of enhanced bioavailability. However, these benefits must be balanced against the possibility of degradation of thermolabile drugs and the absence of a core knowledge base within the pharmaceutical industry with regard to the optimization of the melt-granulation process. Indeed, while the wet-granulation process has been studied
extensively in pharmaceutical and bulk chemical manufacture (Krycer et al. 1980), there is a paucity of information available with regard to the predictability and modelling of the FHMG, a deficit that must be addressed.

6. Conclusion

HME and FHMG are two highly dynamic, interdisciplinary topics that provide a creative link between engineering and pharmaceutical sciences for the purposes of drug delivery. Research in these vibrant research areas is making significant advances resulting in innovative, engineered drug delivery systems. These new scientific discoveries have significant potential for industrial exploitation providing an ‘ideas factory’ for future product developments. Moreover, focus in these key areas will ensure a constant stream of highly trained individuals with an interdisciplinary background and an ability to foster ‘out-of-the-box’ thinking, making them highly suitable for employment within an ever-changing pharmaceutical industry and more importantly capable of going significantly beyond the state of the art to confront major research challenges.

References


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Dr Gavin P. Andrews graduated from Queen’s University Belfast (QUB) with a BSc in chemistry in 1998 and was awarded an MSc in polymer engineering in 1999. After receiving a PhD in pharmaceutics for a thesis entitled ‘The physicochemical characterization of polymeric drug delivery platforms’, he was appointed (October 2002) as a research associate in the interdisciplinary Medical Polymers Research Institute (MPRI), QUB. Dr Andrews held this position until January 2004 when he was appointed to a lectureship in pharmaceutics at the School of Pharmacy, QUB. In addition to holding a lectureship post in pharmaceutics, Dr Andrews is an academic partner of MPRI, a position that enables him to maintain a strong relationship with industry, and is a member and chartered chemist (CChem) of the Royal Society of Chemistry and a chartered scientist (CSci) of the Science Council.

Dr Andrews’ research interests are focused on the combination of cutting edge engineering technologies with fundamental pharmaceutical science to manufacture innovative oral drug delivery platforms and medical devices. Dr Andrews’ research portfolio includes physicochemical characterization of novel polymeric networks, drug–excipient interactions and strategies to improve the performance of both implanted drug delivery systems and orally administered solid dosage forms.

Dr Andrews’ research has received considerable funding from the pharmaceutical industry, EU, Wellcome Trust, Gates Foundation (USA) and EPSRC. More recently, Dr Andrews received a competitive Promising Young Researchers to work alongside Prof. McGinity as a visiting scientist at the University of Texas at Austin. While still at an early stage in his career, Dr Andrews has authored over 40 publications in the area of pharmaceutics and pharmaceutical technology, co-authored a monograph for the Handbook of Pharmaceutical Excipients and has received competitive awards to present his research findings at both national and international conferences.

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