Maria Inês Carvalho Versos Barata

EMERGING TRENDS IN PHARMACEUTICAL MANUFACTURING TECHNOLOGY

Dissertation of Pharmaceutical Biotechnology Master Degree presented to Faculty of Pharmacy of University of Coimbra
Advisers:
Dr. Cláudia Sousa Silva and Prof. Dr. Sérgio Paulo Magalhães Simões

Setembro de 2015

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FFUC FACULDADE DE FARMÁCIA
UNIVERSIDADE DE COIMBRA

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EPIGRAPH

"Recomeça...

Se puderes,

Sem angústia e sem pressa.

E os passos que deres,

Nesse caminho duro

Do futuro,

Dá-os em liberdade.

Enquanto não alcances

Não descanses.

De nenhum fruto queiras só metade.

E, nunca saciando,

Vai colhendo

Ilusões sucessivas no pomar.

Sempre a sonhar

E vendo,

Acordado,

O logro da aventura.

És homem, não te esqueças!

Só é tua a loucura

Onde, com lucidez, te reconheças."

Miguel Torga, Diário XII

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ABSTRACT

With the extremely high average development costs of innovative medicines, the pharmaceutical industry faces unprecedented challenges and is under constant pressure to optimize the drug development process, as consequence of increased competition and healthcare costs. Rapid development of the emerging markets, progress in drug research, the rise in generics production, the availability of high-potency drugs and innovation in manufacturing process will sustainably modify the global pharmaceutical landscape.

Thus, the global process of pharmaceutical innovation is not only focused on developing new drug entities but also in new manufacturing processes, that can optimize this stage of drug development, making it more efficient and cost-effective, responding to felt needs in the pharmaceutical sector. Improvements in process product development approaches and streamlining of manufacturing operations can have a profound impact on the bottomline.

To keep pace with advances of new formulations and the increasing number of highly potent drugs, and so on, engineering expertise is required to design equipment that can manufacture, and package such medicines according to the required specifications while ensuring the safety of the workers.

The aim of this study is to describe new manufacturing processes used in the pharmaceutical industry with particular interest in the following techniques: Fluidized Hot Melt Granulation, Hot Melt Extrusion, Spray Drying Technology, Liquid Dispensing Technology and DiffCORE Technology.

For each one of these manufacturing techniques, a description of the state of the art is given and the pharmaceutical applications, the equipment, the excipients and the advantages and limitations are described.

Keywords: Emerging Techniques in Pharmaceutical Manufacturing, Continuous Processing, Quality-by-Design, Process Analytical Technologies, Fluidized Hot Melt Granulation, Hot Melt Extrusion, Spray Drying Technology, Liquid Dispensing Technology, DiffCORE Technology

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LIST OF ABBREVIATIONS

AE	Adverse Events
CAGR	Compound Annual Growth Rate
CMC	Chemistry Manufacturing and Controls
CQA	Critical Quality Attributes
DS	Drug Substance
EC	Ethylcellulose
EDTA	Ethylenediamine tetraacetic acid
FDA	United States Food and Drug Administration
FHMG	Fluidized Hot Melt Granulation
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HLB	Hydrophilic-Lipophilic Balance
HME	Hot Melt Extrusion
HPC	Hydroxypropylcellulose
HPMC	Hydroxypropylmethylcellulose
IR	Immediate Release
LDT	Liquid Dispensing Technology
MG	Melt Granulation
MR	Modified Release
NIR	Near-Infrared Spectroscopy
PAT	Process Analytical Technology
PEG	Polyethylene Glycol
PEO	Polyethylene Oxide
PPE	Personal Protective Equipment
PVP	Polyvinylpyrrolidone

QbD	Quality-by-Design
R&D	Research and Development
ROI	Return of Investment
SOP	Standard Operating Procedure
SR	Slow Release

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1. Introduction

1 INTRODUCTION

1.1 FACING THE PHARMACEUTICAL FUTURE

The pharmaceutical industry is facing a variety of new and complex challenges in the face of globalization and changing market dynamics. The past decades have witnessed a decline in the discovery, approval and marketing of new chemical entities with fewer blockbuster drugs making their way into the market [1].

The production of a drug product is highly iterative and controls must be established for each lot, from scale-up through commercialization of the final approved product. Effective scale-up of drug product requires collaboration across many interrelated activities and dependences and should consider the analysis of the drug product value chain, including suppliers, materials, equipment and process [2].

According to a recent survey, the global annual spending on pharmaceuticals is set to reach almost §1.2 trillion U.S. dollars in 2016. Due to an increasing cost pressure and increased local demand, production is being relocated to the emerging markets, such as Latin America, Africa, Middle East and Russia. At the same time, the availability of high-potency treatments has also exploded in the past decade and is projected to grow at a compound annual growth rate (CAGR) of 9,9% through 2018 [3]. The rise in generics production is other factor that will sustainably modify the global pharmaceutical landscape [3, 4]. Thus, the market realities in the 21st Century require manufacturing operations to be an externally supportive and to contribute directly to the competitive advantage of the pharmaceutical enterprise [5].

However, over the last decades, the mind-set has evolved among many pharmaceutical business leaders and others that manufacturing is no longer a necessary "strategic competency" [6]. Consequently, pharmaceutical manufacturing has been managed with an internally neutral "cause no problems" mentality. This attitude has resulted in the growth of inefficiencies in several areas, resulting in today's unacceptable high costs of compliance [5]. Moreover, the pharma manufacturing economics have not changed most in the last few decades: gains in pharma production have been modest, market by the recent use of lean production techniques to cut variable costs and boost labor productivity.

The pharma industry stands out among the other manufacturing industries by the astronomical amounts it spends every year on research and development, a stark contrast to the relatively low-tech level of manufacturing industries. For example, in 2004, one company has built a new $90 million manufacturing facility to help produce the key ingredient in a product that was in Phase III and without knowing if it will reach the market or if it will fall to meet the safety and efficacy requirements. At the same time, other company has invested over $1.5 billion in what is to become the world's largest biopharmaceutical facility that will provide global supply of just two products [2, 7].

In addition to the high investments in this sector, the pharmaceutical industry endures losses of approximately $50 billion/year in manufacturing costs from inefficient processes – equivalent to the cost of developing 80 to 90 new drugs every year [8, 9]. Due to high costs of pharmaceutical manufacturing, pharma industry is looking at more holistic approaches to improve the process of bringing new products to the market that can accelerate product development while lowering operational costs.

In fact, US Food and Drug Administration (FDA) has concluded that pharmaceutical operations are inefficient and costly. Compared to other industrial sectors, the rate of introduction of modern engineering process design principles, new measurement and control technologies, and knowledge management systems is low. Indeed, the cost of low efficiency is generally not understood or appreciated (e.g. manufacturing costs can far exceed those for research and development operations in innovative pharmaceutical firms). Low efficiency is predominantly due to "self-imposed" constraints in the system (e.g. static manufacturing processes, focus on testing as opposed to quality-by-design, approach to specifications based on discrete or so called "zero tolerance" criteria, a less than optimal understanding of variability, etc.). In many cases, pharmaceutical process lack advanced on-line quality control systems and rely only on numerous off-line process controls [10]. These constrains keep the system in a corrective action mode. Additionally, this report has also concluded that opportunities for improving efficiency and quality assurance are not generally well recognized [9].

For these reasons, regulators have encouraged the industry to embrace concepts such as Continuous processing, Quality-by-Design (QbD) and the use of advanced process analytical technology (PAT) to produce pharmaceuticals with a higher assurance of acceptable quality at the time and place of manufacture [10].

1.2 EMERGING TRENDS IN PHARMACEUTICAL MANUFACTURING

1.2.1 BATCH PROCESSING VS. CONTINUOUS PROCESSING

The pharmaceutical industry is looking to continuous processing to enhance production efficiency and product quality, in line with recent guidances from regulatory agencies [11]. Decreased fluctuations in production, higher yields, and more profitable processes with lower costs for operation, equipment, and investment are the key factors for greater competitiveness in this sector. One of the most critical points is continuous utilization of product capacity [12, 13].

While most other manufacturing industries use continuous operations combined with advanced process control and automation, the pharmaceutical industry has most relied on batch processing. In contrast, the development of novel manufacturing technologies for pharmaceuticals products has the potential to transform the current batch manufacturing process into a "novel" integrated continuous manufacturing [14].

Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. These improvements along with the adoption of the QbD paradigm for pharmaceutical development and the advancement of PAT for designing, analyzing and controlling manufacturing have contributed to the development of scientific and regulatory readiness for continuous manufacturing [15].

By definition, in conventional processes, the raw materials are charged into a system at the beginning of the process and the product is discharged all at once later. No ingredients cross the system boundaries between the time the raw material is charged and the time the product is discharged. In this type of process, materials from one step are usually tested off-line as per the in-process controls and stored before they are sent to the next step. If the in-process material does not meet quality requirements, it will be discarded or, under certain circumstances, reprocessed prior to moving to the next step [16]. In other words, the batch process is a single or multistage process in which certain quantities of inputs (raw materials) are fed into the processing system unit under conditions suitable (e.g. temperature, time, etc.) for obtaining the desired output. This means that in batch processing various take place in the wake of which a concentration of raw materials and product varies so long as the reaction progresses. At the conclusion of the process the resulting output is removed from

the processing system and will be conducted for other steps required in the manufacturing process, if needed. Moreover, in batch process so long as the batch has not undergone the entire series of actions, there is no possibility of preparing a further batch [17].

On the other hand, in continuous processes the raw materials are continuously charged at a constant rate into the processing system and, at the same time, the products are constantly discharged from the system, throughout the duration of the process (Figure 1.1). Thus, the concentration of raw materials and products remains approximately the same, at every location in the system [17]. This means that, in continuous processing, all the stages are carried out simultaneously (although possibly in different parts of the system) and materials produced during each process step are sent directly and continuously to the next step for further processing [15, 16].

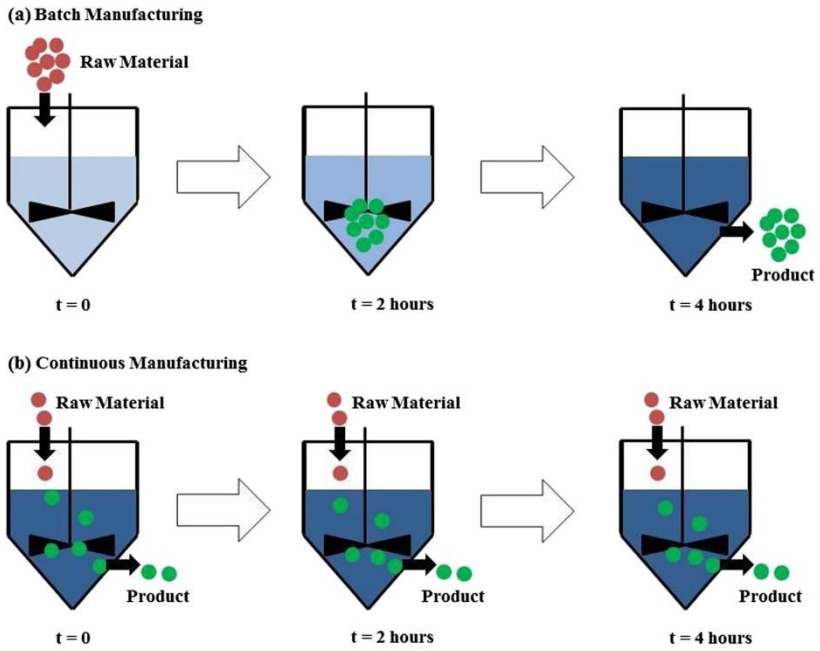


FIGURE 1.1 COMPARISON BETWEEN BATCH MANUFACTURING (A) AND CONTINUOUS MANUFACTURING (B) (ADAPTED FROM LEE, S., 2015 [15]

In fact, current manufacturing practice consists of a series of lengthy and segmented batch process steps often performed in different facilities around the world including isolation, testing, storage and transportation of the various chemical intermediates as well as the drug substance (DS). Because of this disconnection between DS and drug product, there is often limited feedback from downstream operators on the desired DS's physicochemical properties to facilitate its downstream processing [18]. This practice typically leads to a number of "correction steps" that need to be applied to formulate the DS into a an

acceptable dosage form, meeting all the required specifications (Figure 1.2) [14]. An example for these corrective actions is the increase of sizing steps (e.g. granulation, milling) if the product does not meet the desired size [15].

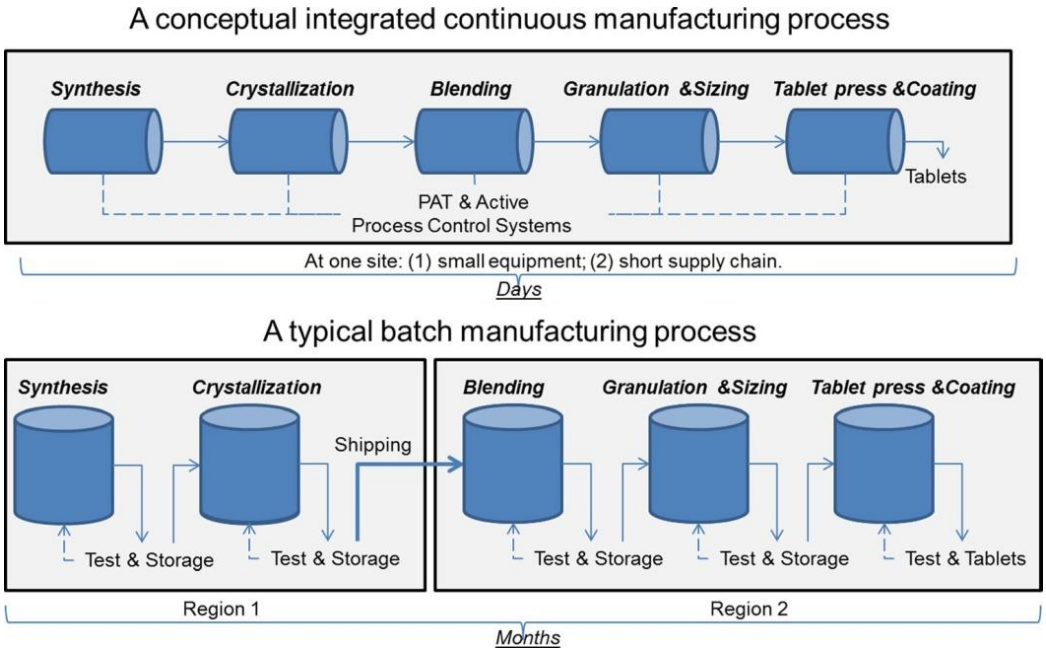


FIGURE 1.2 COMPARISON BETWEEN A CONCEPTUAL INTEGRATED CONTINUOUS MANUFACTURING PROCESS AND A TYPICAL BATCH MANUFACTURING PROCESS (ADAPTED FROM LEE, S., 2015 [15])

Compared to batch manufacturing, continuous processing often involves a higher level of process design to ensure adequate process control and product quality. The benefits provided by continuous processing including an integrated process with fewer steps (e.g. safer, faster response timers, more efficient, shorter times), smaller equipment footprint (e.g. potentially small DS requirements, more flexibility, lower cost, environmental friendly), an enhanced development approach (QbD), real time product quality information and easier change in scale to accommodate supply needs [19, 20]. Indeed, it is estimated that companies that operate with continuous-manufacturing will anticipate a fast return of investment (ROI) and will save 30% or more in operation costs. One reason is that continuous-manufacturing plants are expected to cost much less than the $150 million that a traditional drug-making factory costs because they require less equipment and less space [21, 22].

Moreover, continuous manufacturing also provides an opportunity to utilize this enhanced product and process understanding to adopt advanced manufacturing controls to produce uniformly high-quality products with reduced waste resulting from the generation of out-of-specification material [23]. As such, this can help to improve production system with more energy-efficient operations and reduced carbon footprints. At least, the flexibility of continuous manufacturing offers major advantages in terms of profitability at the other stages of product life cycle. Once the product is launched, capacity can be dynamically adjusted to match market requirements [22]. Table 1.1 summarizes some features of continuous manufacturing and potential benefits.

TABLE 1.1 FEATURES AND POTENTIAL BENEFITS OF CONTINUOUS MANUFACTURING (ADAPTED FROM LEE, S.; 2015 [15]).

Features of continuous manufacturing	**Benefits**
Small equipment and space required	Efficient Reduced safety hazards
Short supply chains	No storage/shipping for intermediates Fast response to market storage Less degradation for sensitive intermediates
All key characteristics should be roughly constant at any time	Lower batch-to-batch variations Possible elimination of downstream corrective steps Simply to development process monitoring systems and control strategies
No batch handling	Reduction of operators on site Increased operator safety
Continuous flow production	Easy to scale-up

In fact, continuous unit operations are generally more efficient than their batch counterparts and offer much higher throughput per volume and per unit time, thereby often greatly reducing the size of the processing equipment [15]. Furthermore, the small scale of continuous manufacturing can decrease the safety hazards associated with highly energetic or hazardous materials and potentially more flexibility in the use of non-specialized manufacturing facilities [24].

Due to economic factors, supply chains for main drug substances and excipients span several countries and contain multiple supply vulnerabilities. Under batch processing steps, intermediates may not be immediately processed and, consequently, they are stored in containers and shipped for the next manufacturing facility. Continuous manufacturing allows the production at various scales with a given process and eliminate hold times between steps, which is particularly important for sensitive materials [15].

The continuous processing flow of this emerging trend on pharmaceutical manufacturing promotes lower batch-to-batch variation and a reduction of operators on site [25].

Additionally, continuous manufacturing facilitates the scale-up. Indeed, operating the process for longer periods or increasing the flow rate through the process are some scale-up options [19, 26].

1.2.2 Quality-by-Design

As stated before, continuous manufacturing is strongly aligned with FDA's support of the QbD paradigm for pharmaceutical development. According to QbD, most quality problems are a result of the way that quality was planned (or not planned) in the first place [27]. Thus, QbD is a systematic scientific and risk-based approach to pharmaceutical development that advises companies to demonstrate product and process understanding and to use this understanding to implement effective quality control strategies to achieve a predefined objective [15]. In other words, this risk-based approach emphasizes process design and identifies what is critical for product quality, including what to control, when and how [27].

In fact, when compared to the traditional approach of pharmaceutical manufacturing, QbD makes the process more adjustable, since it is based on designing and developing formulations and manufacturing processes to ensure predefined product quality [28]. This approach also implies a real-time process control, which contrast with traditional approach based on off-line analysis of batch data. Moreover, identifying the critical controls for each process step, QbD contributes for a risk-based approach that consequently promotes a continuous improvement. Avoiding a problem-reactive approach, QbD will prevent possible post-approval changes that are characteristics of a traditional approach (Table 1.2) [1, 28].

TABLE 1.2 COMPARISON BETWEEN TRADITIONAL APPROACH AND QBD AT VARIOUS STAGES OF PHARMACEUTICAL DEVELOPMENT (ADAPTED FROM HUMPHREY, D.; 2012 [27])

Aspect	Traditional	Quality by Design
Pharmaceutical Development	Empirical	Systematic
Manufacturing Process	Fixed	Adjustable
Process Control	Offline Analysis	PAT utilized for feedback for real-time
Product Specification	Primary means of quality control; based on batch data.	Part of the overall quality control strategy; based on desired product performance
Control Strategy	Mainly by intermediate and end product testing	Risk-based; Controls shifted up-stream; Real-time release
Lifecycle management	Reactive to problems; Post-approval changes needed	Continual improvement

Understanding and implementation QbD will enhance and modernize the regulation of pharmaceutical manufacturing and product quality and it will transform the Chemistry, Manufacturing and Controls (CMC) regulatory review into a modern science-based pharmaceutical quality assessment [28].

1.2.3 PROCESS ANALYTICAL TECHNOLOGY

Continuous improvement is an essential element in a modern quality system and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. [9].

PAT refers to the measurement and evaluation tools that enable QbD. In support of QbD, PAT's goal is to ensure final product quality by designing, analyzing, and controlling process variability through timely measurements of critical quality and performance attributes of raw and in-process materials. This applies not only to manufacturing process

but also to all development process. With in-line analytics, product developers can gain a much higher and faster understanding of the process than is possible with offline analysis (e.g. a manual sampling) [27, 29].

There are many tools available that enable process understanding for scientific, risk-managed, pharmaceutical development, manufacture, and quality assurance. These tools, when used within a system, can provide effective and efficient means for acquiring information to facilitate process understanding, continuous improvement and development of risk-mitigation strategies [29]. In PAT framework, these tools can be categorized in multivariate data acquisition and analysis, process analytical chemistry tools, process monitoring and control and, at least, continuous process optimization and knowledge management [30]. Multivariate data acquisition and analysis requires building scientific understanding about a process and identifying critical material attributes and process parameters that affect product quality and integrating this knowledge into the process control, which is essentially the same as the process understanding in the context of QbD. Process analytical chemistry tools provide real-time and in situ data about the status of the process. Multivariate data analysis takes the raw information from the PAT tools and connects it to critical quality attributes (CQAs). Based on the outcome of the data analysis, process controls adjust critical variables to assure that CQAs are met [31, 32].

Introducing PAT has a considerable positive impact on reducing production costs. It speeds up decisions at the unit operation level and improves the quality and efficiency of process steps, leading to shorter batch runs and increased quality consistency [22]. By providing continuous, real-time quality information, PAT contributes to continuous processing, allowing constant quality checks along the way that eliminate the need for a final quality check to release a batch [1]. Hence, the real-time access to information offered by PAT is invaluable during pharmaceutical development and during the scale-up to commercial production [1, 27].

1.3 Overview of Pharmaceutical Manufacturing

As stated before, pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles. Effective use of the most current pharmaceutical science and engineering principles and knowledge – throughout a life cycle of

a product – can improve the efficiencies of both the manufacturing and regulatory processes. Therefore, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries and ways of doing business [29].

In the following chapters will be described non-conventional manufacturing process in the pharmaceutical industry that apply some of the trends herein – Continuous manufacturing, QbD, PAT – and bring innovation to this sector.

The presentation of each technique will include an analysis of the processing step involved, including the critical steps and the equipment/materials needed. The advantages and limitations of each technique presented as well as their applications in the pharmaceutical sector will also be addressed.

2. Fluidized Hot Melt Granulation

2 FLUIDIZED HOT MELT GRANULATION

Fluidized Hot Melt Granulation (FHMG) is a novel technology for granulation process in pharmaceutical industry, with several advantages over other commercial granulation techniques [33].

Pharmaceutical granulation 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 [34, 35]. Conventionally, granulation processes are employed within pharmaceutical industry to agglomerate and mix powders to produce granules of the desire shape and size, factors that are pertinent to overall tabletability [36]. In most cases, granules are intermediate products and typically fall within the size range of 0.1 – 3 mm. The DS may first be granulated on its own and then blended with other excipients or, alternatively, may be co-granulated with most or all of the excipients [37, 38]. During granulation process powder particles adhere to one another to form agglomerates and the size of the particle is increased [39].

To a better understand of FHMG technique, a general overview of existing granulation techniques should be given.

The granulation technique may be widely categorized in two types, dry granulation (slugging and roller compaction) and wet granulation (high shear mixing, fluidized bed granulation and wet extrusion), based on the type of method used to facilitate the agglomeration of powder particles (Figure 2.1) [40]. Thereafter, to overcome some limitations associated with these granulation techniques has been developed other technology, melt granulation, which will also described in this chapter.

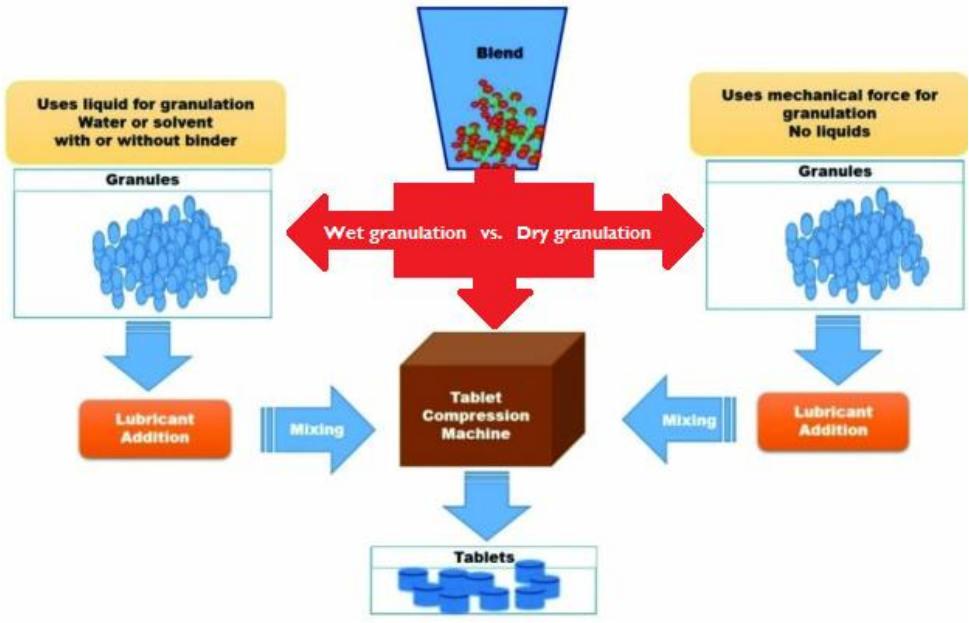


FIGURE 2.1 SCHEMATIC DIAGRAM OF COMPARISON BETWEEN DRY AND WET GRANULATION (ADAPTED FROM SHANMUGAM, S.; 2015 [40]

The distinguishing factor of these techniques is that dry granulation uses mechanical compression or compaction to facilitate the agglomeration of dry powder particles, while the wet granulation uses granulation liquid to facilitate the agglomeration by formation of wet mass by adhesion [40].

The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties.

Table 2.1 lists the most common granulation techniques in the pharmaceutical industry [41].

TABLE 2.1 FREQUENTLY USED GRANULATION TECHNIQUES ANS SUBSEQUENT PROCESSING (ADAPTED FROM PARKH, D, 2009 [41])

	Process	**Subsequence processing** (examples)
Dry granulation	Roller compaction	Mill; Blend
	Slugging	Recompress; mill; blend
Wet granulation	High-shear mixer	Fluid-bed dry; mill; blend
	Fluidized bed	Mill; blend

DRY GRANULATION

Dry granulation is a controlled crushing of pre-compacted powders densified by either slugging or passing it between two counter-rotating rolls - roller compaction [42].

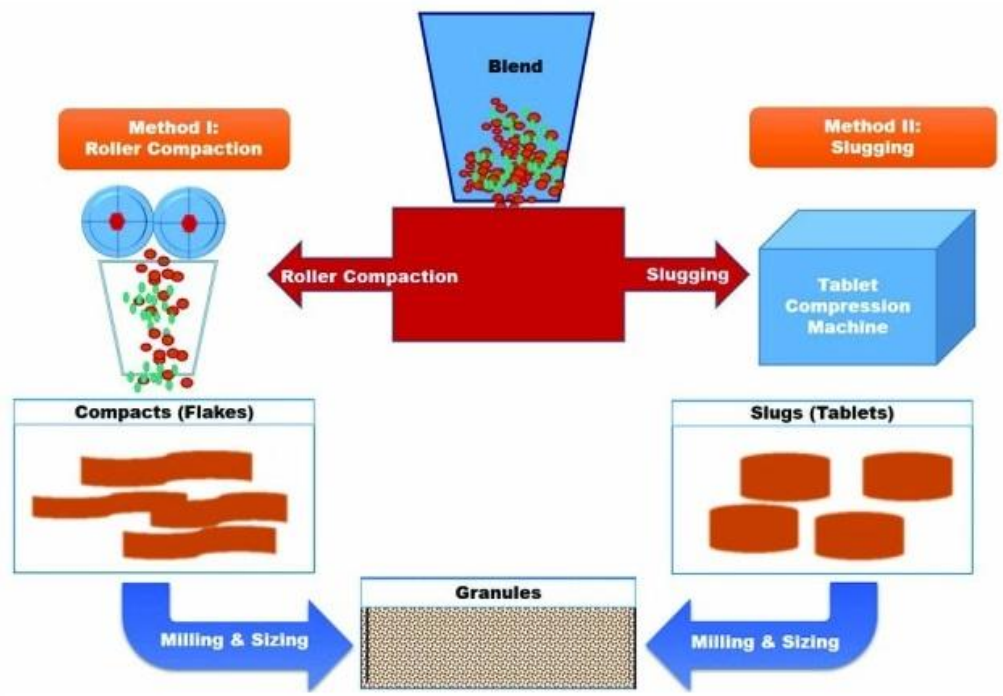


FIGURE 2.2 SCHEMATIC DIAGRAM OF DRY GRANULATION BY TWO DIFFERENT METHODS: SLUGGING AND ROLLER COMPACTION (ADAPTED FROM SHANMUGAM, S., 2015 [40]).

Slugging is a pre-compression process for the formation of extra-large tablets (slugs), usually of variable weight, due to poor flow of the drug powder. The resulting slugs are subsequently broken into granules and could be recompressed to obtain the final tablets [43].

In contrast, roller compaction is a cost effective alternative where the material is densified between two counter rotating rolls under pressure forming a compact ribbon, which is milled into granules. This fairly simple technique is especially applicable for voluminous materials as it greatly enhances the bulk density. The disadvantages of the roller compaction comprise the formation of a relative large amount of dust and fines and the decrease in the compaction properties of powder [44].

In general, dry techniques have smaller process times and avoid wetting and drying processes. It is also advantageous for manufacturing of heat sensitive material and for improving disintegration since powder particles are not bonded together by a binder. Dry granulation does not permit uniform color distribution and tends to create more dust, increasing the potential contamination, which is the major limitation of this method [45].

WET GRANULATION

Regarding to the wet granulation, granules are produced by wet massing of the excipients and DS with granulation liquid with or without binder (Figure 2.3).

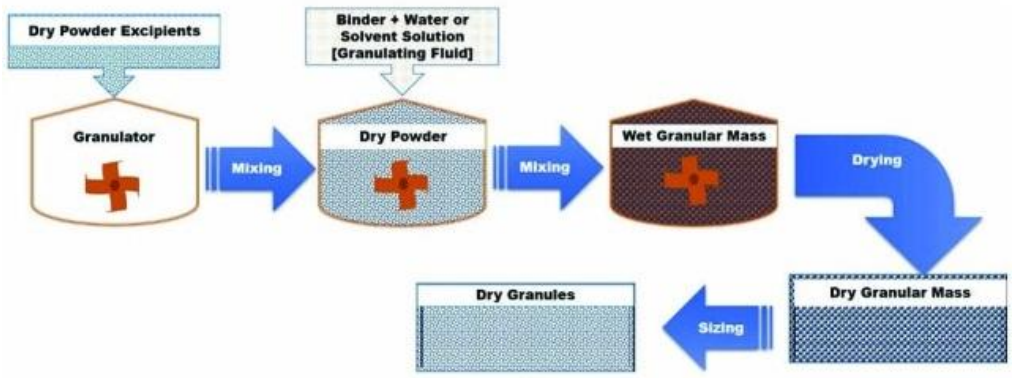


FIGURE 2.3 SCHEMATIC DIAGRAM OF CONVENTIONAL WET GRANULATION (ADAPTED FROM SHANMUGAM, S., 2015 [40])

High-shear wet granulation is performed in continuous mode using twin screw granulators, characterized by a modular screw profile including a sequence of different screw elements with various shapes, orientation and function. In this process, wet granulation is accompanied by high mechanical agitation by an impeller and a chopper. Mixing, densification and agglomeration are achieved through shear and compaction force exerted by the impeller [46].

In fluidized-bed granulation, the powder is maintained in a fluidized state by a flow of air injected upward through a distributor plate at the base of granulator. Escape of the granulation material is prevented by exhaust filters, which can be agitated to reintroduce material into the bed. The liquid binder is sprayed through a nozzle onto the top of the bed

or through a draft tube insert on the bed bottom. The granules formation is result of adhesion of solid particles to the liquid droplets [47, 48].

Wet granulation is the most widespread granulation technique despite the fact it involves multiple unit processes such as wet massing, drying and screening, which are complex, time consuming, and expensive requiring large space and multiple equipment [40, 41, 49]. Moreover, wet techniques cannot be applied to drugs that are unstable when moist [50]. Consequently, it is well accepted that a novel process able to circumvent such difficulties would be highly superior and could dramatically improve particle processing to ensure acceptable and reproducible pharmaceutical granules [51].

MELT GRANULATION

Melt granulation (MG) is a size enlargement process in which the addition of a binder that melts or softens at relatively low temperatures is used to achieve agglomeration of solid particles in formulation. The process utilizes materials that are effective as granulating agents when they are in the softened or molten materials complete the granulation process (Figure 2.4) [52].

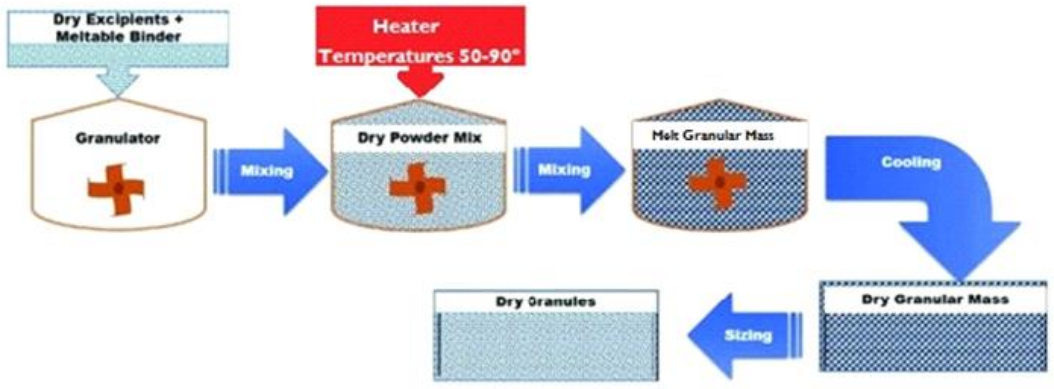


FIGURE 2.4 SCHEMATIC DIAGRAM OF MELT GRANULATION (ADAPTED FROM SHANMUGAM, S., 2015 [40]).

It has been reported that binders that melt in the range of 50°-90° C are suitable for meltable granulation [53]. This specific temperature interval can be justified due to the

requirements for the formulation during processing and storage. In fact, for melt granulation purposes most of the binders used have a melting point above 50°C to avoid softening of the dosage form during storage and to maintain the structural integrity of the matrix at body temperature, in cases of sustained-release drug delivery upon oral administration. Binders with a melting point above 90°C are seldom used to avoid thermal degradation of the active during processing and to limit process time and energy consumption [41].

The process of melt granulation consists of a combination of three different phases: wetting and nucleation, coalescence step and attrition/breakage. During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates. The next step (coalescence step) involves nuclei that have residual surface liquid to promote successful fusion of nuclei. Attrition and breakage refers to granulation fragmentation, where solidification occurs by tray cooling to ambient temperature [54].

Agglomerate formation during melt granulation occurs by immersion (Figure 2.5), distribution (Figure 2.6) or through a combination of both and the prevalence of one or the other mechanism is mainly governed by the ratio between the size of molten binder droplets and size of solid particles [55, 56].

When the binder droplet is large compared to the particles, nucleation will occur by immersion of smaller particles into the larger drop [57]. Immersion begins with binder particle as a core of the agglomerate, to which finer particles are attached and embedded (see Figure 2.5). Immersion growth, and subsequent layering, is attractive from the viewpoint that agglomerate growth may be controlled by the core binder size, and the microstructure of the immersion granule is layer – layer structured, which may have significant potential for pharmaceutical applications [58]. This produces nuclei with saturated pores. The viscosity of the binder affects how easily the particles, attached outside of the binder drop, can migrate to the surface [33].

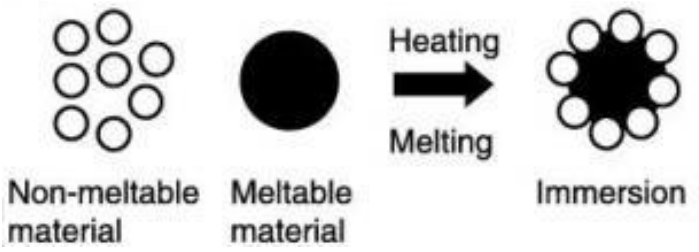


FIGURE 2.5 AGGLOMERATE FORMATION BY IMMERSION (ADAPTED FROM SUTHAR, A.; 2009 [59]).

In contrast, if relatively small droplets of binder (<250 μm) are present and are not greater than the solid particles, the nucleation will occur by the distribution of the molten binder droplets on particle surface of the particles, which will then start to coalesce and hence granule grown. This may cause the nuclei to have trapped air and thus increase voidage (Figure 2.6) [33].

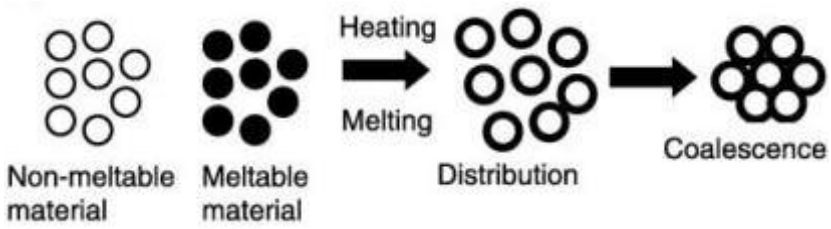


FIGURE 2.6 AGGLOMERATE FORMATION BY DISTRIBUTION (ADAPTED FROM SUTHAR, A.; 2009 [59]).

Over the last decade, MG has received increasing attention because aqueous or organic solvents are not required which circumvents the problems associated with in-process hydrolysis and solvent removal [45].

Mainly, high-shear mixers and fluidized-bed granulators have been used for melt granulation purposes.

Nowadays, the most commonly used equipment for melt granulation is a high-shear mixer [60, 61], in which the binder is added either in the powder form to the starting materials at ambient temperature followed by heating to above the melting point of the binder or in molten form to the heated materials (Figure 2.7). Melting is achieved by the energy added through the mixer friction and the heated jacket of the bowl [62].

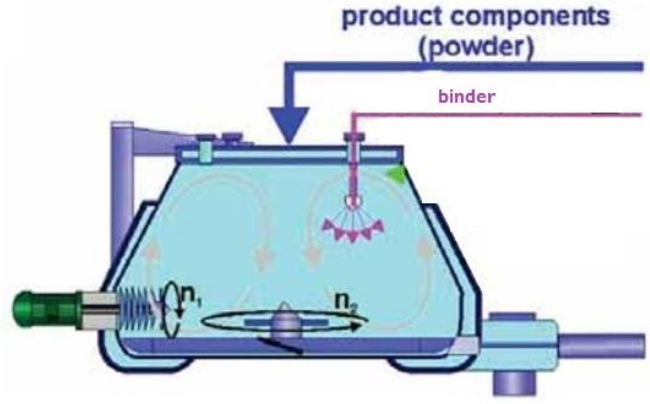


FIGURE 2.7 SCHEME OF MELT GRANULATION USING A HIGH-SHEAR MIXER (ADAPTED FROM GLATT GMBH, 2007 [63]).

The granule quality produced by high-shear melt granulation depends on parameters such as binder content, binder type, particle size, binder rheology, powder cohesivity, product temperature, jacket temperature, atomization pressure, mixing time, impeller speed and properties of solid nonmeltable particles [41].

Fluidized Hot Melt Granulation

In addition to shear granulators, fluidized methods, such as fluidized beds, have been developed for melt granulation purposes [64].

Fluidized bed granulation is a suitable method to prepare granules for tableting, because the lack of any shear force during granulation results in porous granules with low strength [65, 66]. 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 [67].

In this context, FHMG is emerging as an innovative technique for the preparation of pharmaceutical granules of a suitable size and compression profile for subsequent processing into high-performance solid dosage forms [34, 67]. FHMG differs from normal melt granulation using fluidized beds because it uses solid binders initially, which then are fluidized using hot air, which melted the binder and promoted granulation. Normal fluidized melt process spray a molten binder through a nozzle onto a bed of fluidized solid particles.

This novel melt granulation process combines the advantages of both dry and wet granulation methods, and represents an innovative continuous granulation process capable of mixing and agglomerating excipients and drug substance to produce uniform blends of particles suitable for use in the pharmaceutical manufacturing wherein the properties of the DS or excipients are not suitable for standard granulation techniques [45, 68].

2.1 Pharmaceutical Applications

As referred before, FHMG is particularly suitable for drugs unstable in solution, and an appropriate choice of the granulation excipients may allow controlling drug release rate [34, 64, 69]. Previous studies have employed FHMG for the preparation of granules with excellent flow characteristics and suitability for processing into tablets, capsules, granules and/or pellets [70].

Furthermore, FHMG has been shown to have the capability to make fine, taste-masked granules containing a bitter drug substance, as well as being useful for making a controlled release formulation and enteric dosage formulations [50, 71-73].

2.2 Equipment and Process Technology

Pharmaceutical granulation encompasses a large number of processes designed to agglomerate a powder mass together and it is a classic example of particle design, whereby the characteristics of the resultant agglomerates are carefully tailored using a unique combination of formulation design and process design [45].

As stated before and similar to other melt granulation techniques, FHMG is a process by which pharmaceutical powders are agglomerated using low melting point excipients as binders instead of traditional liquid binders, in a fluid bed of hot air [58, 64].

In FHMG, a molten binder, DS and other functional excipients are heated together in a fluidized bed system; when the granules are cooled to the solid state (also within the fluidized bed) it is found that the molten binder acts to form solid bridges resulting in a consolidated granule [45]. The meltable binders are added to the system either as a molten liquid or a solid that melts during the process. The system provides heat continuously to maintain the molten state of the binder thus facilitating granulation. The system is subsequently cooled to solidify the binder and harden the granular structure (Figure 2.8) [56].

The meltable binder can be added while processing by two methods. The first is spraying the meltable binder on the powder through a nozzle. The second is incorporating the meltable binder within the powder initially [70].

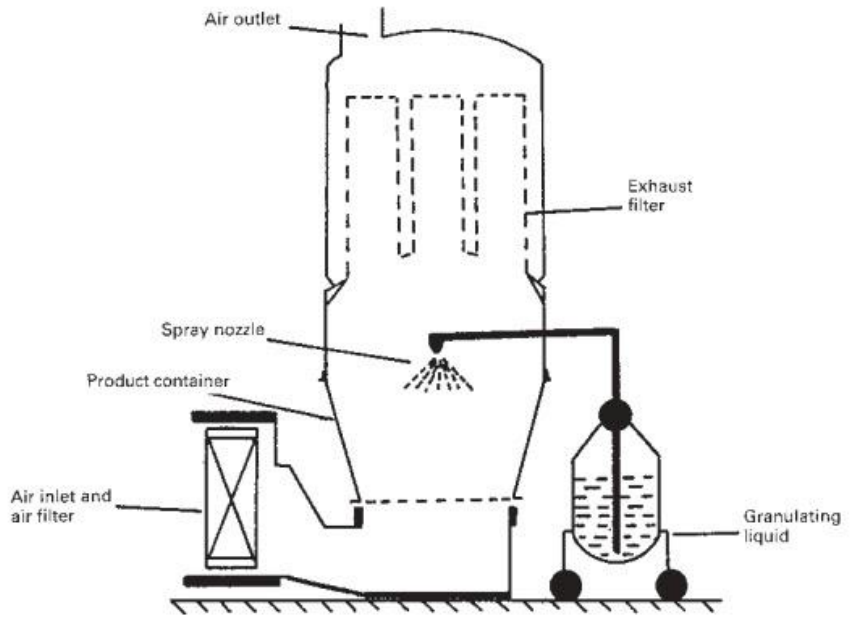


FIGURE 2.8 SCHEME OF FLUIDIZED HOT MELT GRANULATION EQUIPMENT (ADAPTED FROM DACANAL, G. 2008 [74]).

As any new process, identification of the correlation between granule characteristics, process parameters and formulation variables must be established [75]. Similar to other granulation techniques, process parameters known to influence FHMG include: binder content, binder properties, particle size and air flow rate, all of which may influence the final tablet properties [60, 76, 77]. Overall the most important critical variables determining the particle size and granule quality during fluidized hot-melt granulation are concentration of excipients, viscosity, spray rate, droplet/particle size of the binder, primary particle size, bed temperature, atomization pressure, air velocity, and atomization pressure [34, 41, 77, 78].

Several research groups have studied the effect of these process variables on FHMG. One of this research groups has shown that the granule growth mechanism is dependent on the ratio of binder droplet size to powder particle size [60] and that the granule size is directly proportional to liquid mass flow rate [79]. Therefore, the increase of granule size during FHMG is also influenced by viscosity of the binder melt, suggesting that the physical properties of tablets pressed from the fluidized hot melted granules were influenced by the properties of the binder material [50, 76].

In FHMG processes, the determination of characteristic yield properties of the granules within the hot fluidized bed is more complex compared to ambient temperature systems where plastic yield stress can be measured. Within the FHMG process the

characteristic flow stress of the binder-particle slurry is within the limits of the apparent viscosity of the binder and the yield strength of the consolidated granule. However, it seems reasonable to assume (for growth regime modeling) that as FHMG system is operating in excess of the melt temperature of the binder, the apparent viscosity would be a more accurate approximation of the characteristic flow property of the system [34].

2.3 Materials for Fluidized Hot Melt Granulation

Melt granulation, as other techniques have specific requirements such as the melting point of fine solid particles should be at least 20°C higher than that the maximum processing temperature and a meltable binder suitable for melt granulation has a melting point typically within the range of 50-90°C [33]. However, since FHMG involves changing the physical state of the meltable binder, its melting point should be lower than the processing temperature on the fluidized bed.

The selection of meltable binder depends on what is the desired final formulation target profile. Therefore, hydrophilic meltable binders, such as PEGs and poloxamer, are used to prepare immediate-release dosage forms; while hydrophobic meltable binders; such as stearic acid, glyceryl behenate and hydrogenated castor oil, are preferred for prolonged-release formulations [70, 80]. It can be concluded that its hydrophilic-lipophilic balance (HLB) ensures the intended release of the active substance.

Meltable binders require further research, since the application of this type of processing has been limited by the complex behavior of the carriers, associated with their physicochemical properties which can lead to changes in the final product and/or have adverse effects during storage. To overcome these drawbacks, the use of novel fusible excipients has raised special interest in recent years [69].

In particular Gelucires, consisting of mixtures of glycerides and fatty acid esters of PEG, are receiving attention as innovative excipients. These new excipients have shown a better performance in controlled release systems using laboratory melting-solidification techniques compared to conventional meltable binders [81]. The nature and proportion of Gelucires' components determine the HLB and melting point (33-70 °C), both properties with technological and biopharmaceutical impact. Although Gelucires have shown potentialities for the design of floating controlled release matrix systems more research is needed in this area [82, 83].

2.4 Process Main Advantages and Limitations

FHMG presents comparative advantages over conventional granulation methods [84, 85]. FHMG is a simple and rapid granulation technique that may be performed in one step, in contrast to conventional wet granulation whereby transfer from granulator to the drying equipment is usually necessary, thereby involving transfer losses, increasing processing and operator time and increasing dust levels and consequently contamination of equipment with other particles that could affect the quality of final product. Issues that are particularly pertinent to highly potent drugs such as antineoplastic agents and certain hormones, wherein operator exposure to drug must be minimized [68].

Thus, this technology is a good alternative to wet granulation for water-sensitive pharmaceutical powders and also results in savings in energy consumption and operation times since it does not require a drying step and solidification occurs almost instantaneously. In addition, it is particularly suitable for drugs unstable in solution, and an appropriate choice of the granulation excipients may allow controlling drug release rate [34, 64, 69].

The absence of aqueous phase and the use of solvents, potentially negating problems associated with hydrolysis and water removal via heating when using aqueous granulation which favors a higher binder to substrate ratio, and can generate granules with higher density and reduced porosity [68]. Moreover, granules produced via FHMG processes have been shown to possess high levels of fluidity and compressibility facilitating manufacture of solid dosage forms [58].

When compared to melt granulation in high shears mixers, FHMG has also some advantages such as better control of the product temperature, which simplifies the whole process allowing the cooling phase to be performed easily and quickly in the same piece of equipment [57, 70]. Indeed, the energy input during FHMG is almost entirely by the temperature of fluidized air. The shear forces in fluidized bed processing are too low to affect the process temperature, thus minimizing the risk of uncontrolled particle growth due to poor temperature control (that may occur when high-shear mixer is used).

Another important difference between melt granulation using high-shear mixer and FHMG is that when the granulation end point is reached the material in a fluidized bed can be rapidly cooled via fluidizing air. In other hand, the energy stared in a mass contained in high-shear mixer must primarily dissipate via jacket of the mixing bowl, resulting in a longer process time. The less efficient heat transfer during high-shear melting granulation could

cause excessive heating due to the frictional heat generated and/or cause scale-up issues when processing larger batches as the ratio material mass to bowl surface increases [41].

Nevertheless, as other techniques, FHMG has also some limitations. These limitations involve the high energy input required and the characteristics of the meltable binders. Meltable binder should have appropriate melting point; lower melting point binder may melt/soften during handling and higher melting point binders requires high melting temperature and can contribute for instability problems for heat-labile drugs [86].

2.5 A View to the Future

FHMG is a novel granulation process whereby a solid-state binder is added as discreet particles to the fluidized bed becoming molten during the non-ambient process. This technology has significant potential for the preparation of granules with a particle size distribution suitable for subsequent pharmaceutical processing such as tablet pressing and/or capsule filling, but is has not been widely applied because the detailed mechanism [51]. In fact, this technology has been widely studied by several research groups in order to understand the influence of all parameters involved. Indeed, the synchronized combination of sustained release pellet formulation with FHMG as a one-step and one-machine process can have an economical positive interest to pharmaceutical industry [70]. However, it was not possible to find any information regarding marketed drug products produced by this technology. Thus, despite FHMG not being widespread in pharmaceutical industry, this proves to be a very promising technology.

3. Hot melt extrusion

3 HOT-MELT EXTRUSION

Hot-melt extrusion (HME) is one of the most widely used manufacturing processes in the plastic industry since the mid-nineteenth century to prepare polymeric insulation to coating wires. Hot-melt extrusion is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape [87].

The interest in hot-melt extrusion for pharmaceutical applications is evident from the increasing number of patents and publications in scientific literature. The first paper about Hot-melt extrusion may be accredited to Follonier et al. who described the use of this processing technique for the production of pellets that contained high loadings of drugs with high water solubility. Since the publication of this paper, more than two hundred papers have been published on this technology, reflecting the emerging importance of HME to the pharmaceutical industry [88, 89].

Recently, HME technology has been gaining attention as many of its newer advantages are being investigated and applied in the field of pharmaceuticals and drug delivery [90].

Thus, this innovative drug delivery technology is considered a robust method of producing numerous drug delivery systems and the formulation produced by HME can contain a drug dispersed in a matrix at the molecular level forming a solid dispersion, which is very beneficial for poorly soluble drugs [91].

HME involves applying heat, pressure and agitation to a material with the use of a screw in a barrel, which transports the molten material through a die to give it a desired shape [92]. This technology requires a pharmaceutical grade polymer that can be processed at relatively low temperatures due to the thermal sensitivity of many drugs. As both a thermal and mechanical process, hot-melt extrusion applies a significant amount of heat and shear stress on the materials being subjected to the hot-melt extrusion process. As a result, the drug substances and the polymeric carriers may undergo chemical reactions [67]. Then, all components must be thermally stable at the processing temperature during the short duration of the heating process and the chemical properties and the stability of the formulation components must be monitored in order to eliminate any degradation concerns [87].

Within the scope of hot-melt extrusion, mixing is generally categorized into distributive mixing and dispersive mixing. Distributive mixing is capable of promoting

homogeneity of the extruded composition and may contribute to the content uniformity of the formulation.

3.1 Pharmaceutical Applications

Due to the advent of high throughput screening in the drug discovery process, the lead compounds are often high molecular weight and highly lipophilic and, therefore, exhibit poor solubility [93].

Over the last years, it has been demonstrated that HME technology is an innovative and feasible approach for the manufacture of granules, pellets, immediate and modified release tablets and capsules, transdermal/transmucosal films and implantable reservoir devices [90, 94-96].

Briefly, in the pharmaceutical industry HME has been used for various applications such as enhancing the dissolution rate and bioavailability of poorly soluble drugs by forming a solid dispersion or solid solution, controlling or modifying the release of drug, formulation of targeted release dosage forms, taste masking of bitter DSs and formulation of various films [97, 98].

Indeed, HME is an extremely suitable for the formation of solid dispersions, which allow that a poorly water-soluble crystalline form could be converted to an amorphous form, increasing the solubility and bioavailability [99, 100]. Regarding targeted drug delivery, several studies have illustrated the improvements in bioavailability that have been achieved using targeted drug delivery systems formulated via HME processes [101, 102]. HME has also been used as a taste masking technique for bitter active ingredients by the formulation of solid dispersions with a taste masking polymer. These solid dispersions prevent the release of bitter drugs in the saliva and, therefore, prevent the interaction between the drug molecules and taste bud [103, 104]

HME-related patents which have been issued for pharmaceutical applications have steadily increased worldwide, since the early 1980s (Figure 3.1).

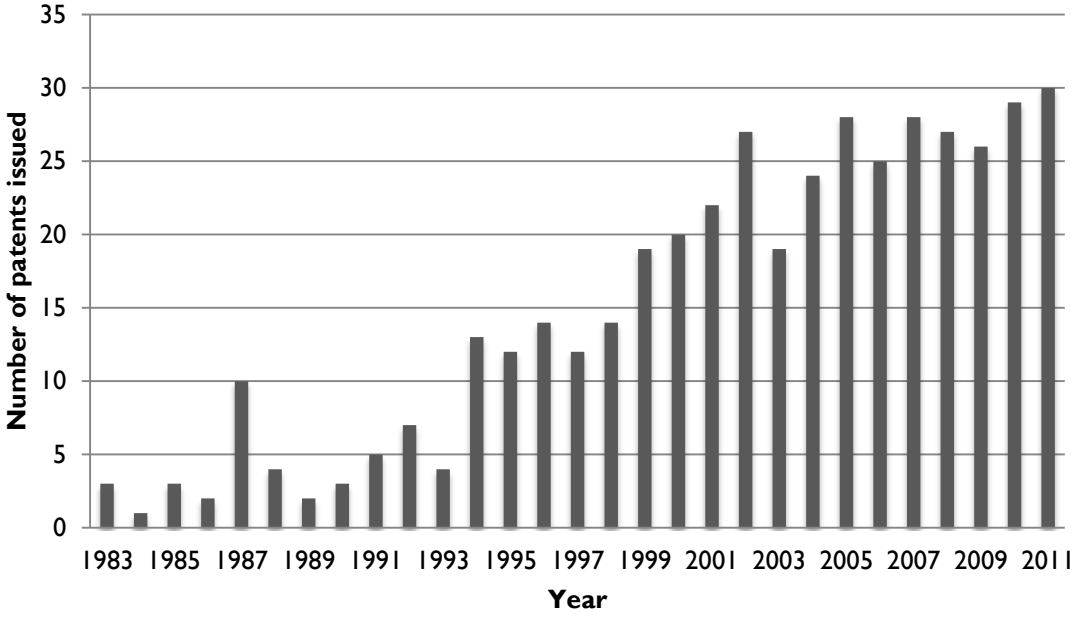


FIGURE 3.1 THE NUMBER OF HOT-MELT EXTRUSION PATENTS ISSUED FOR PHARMACEUTICAL APPLICATIONS. (ADAPTED FROM REPKA,, 2007 [95]).

Heretofore, the USA and Germany hold approximately more than half of all issued patents for HME in the market (Figure 3.2) [92]. It should be noted that it was not possible to find latest data regarding the percentage of HME patents issued by country.

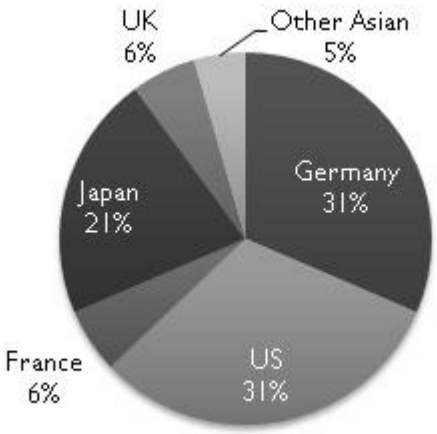


FIGURE 3.2 THE PERCENTAGE OF HOT-MELT EXTRUSION PATENTS ISSUED BY COUNTRY SINCE 1983 FOR PHARMACEUTICAL APPLICATIONS. (ADAPTED FROM CROWLEY AND REPKA, 2007).

As result, several commercial HME products have been successfully marketed (see Table 3.1.) or are now under late-stage development [105].

TABLE 3.1 CURRENTLY MARKETED DRUG PRODUCTS PRODUCED WITH HOT MELT EXTRUSION (ADAPTED FROM LI AND PANG, 2013)

Product	Indication	HME purpose	Company
Lacrisert	Dry eye syndrome	Shaped system	Merck
Zoladex	Prostate cancer	Shaped system	AstraZeneca
Implanon	Contraceptive	Shaped system	Organon
Gris-PEG	Anti-fungal	Crystalline dispersion	Pedinol Pharmacal Inc.
NuvaRing (Circlet)	Contraceptive	Shaped system	Merck
Norvir	Antiviral	Amorphous system	Abbot Lab.
Kaletra	Antiviral	Amorphous system	Abbot Lab.
Eucreas	Diabetes	Melt granulation	Novartis
Zithromax	Antibiotic	Melt congeal	Pfizer
Orzurdex	Macular edema	Shaped system	Life Cycle Pharma
Fenoglide	Dyslipidemia	Solid dispersion	Merck
Posaconazole	Anti-fungal	Amorphous system	Merck

3.2 EQUIPMENT AND PROCESS TECHNOLOGY

As previously stated, HME was first developed in the plastic industry and in its most basic form, compacts, blends, and converts a powder mix into a product of uniform density and shape [106].

Extruders for pharmaceutical industry have been designed and adapted for mixing drugs with carriers in various dosage forms. The significant difference between extruders for thermoplastics and pharmaceutical applications in the equipment used and hence, the contact surface, which must meet regulatory requirements. The contact parts of the extruders used

in pharmaceuticals must not be reactive nor may they release components into the product. The extruder equipment is specially configured to fulfill all cleaning and validation standards applicable to the pharmaceutical industry (Figure 3.3) [107, 108].

FIGURE 3.3 GENERAL OVERVIEW OF AN EXAMPLE OF HOT MELT EXTRUDER (ADAPTED FROM LEISTRITZ, 2015 [102]).

Extrusion is a process which is used to create new materials with desirable properties by manipulating additive ingredients through a number of staged unit operations and forcing the product through defined die geometry, under set conditions such as temperature, pressure, rate of mixing and feed-rate [109]

At the most fundamental level, an extruder consists of a platform that supports a drive system, an extrusion barrel, a rotating screw arranged on the screw shaft and an extrusion die for defining product shape (Figure 3.4) [94, 110]

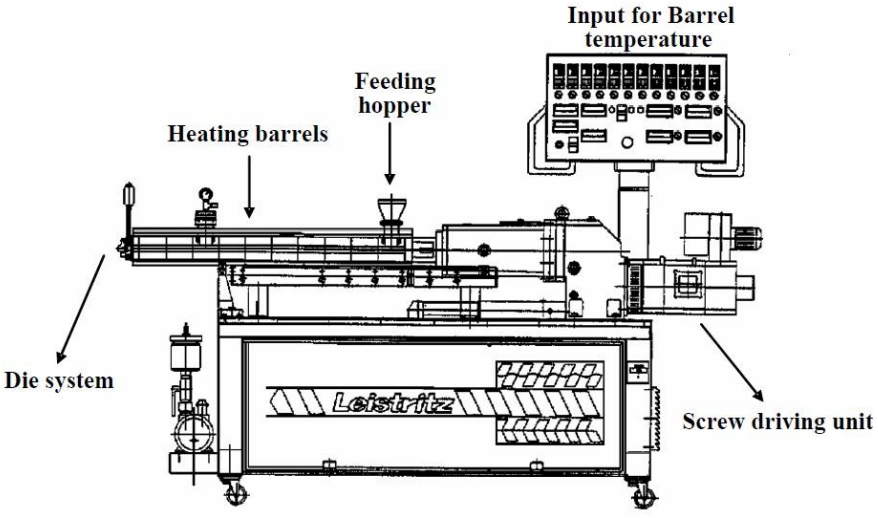


FIGURE 3.4 OVERVIEW OF THE KEY COMPONENTS OF AN HOT MELT EXTRUDER. (ADAPTED FROM NANJWADE, 2011 [104]).

Extrusion systems can be categorized as ram extrusion or screw extrusion (single screw and twin screw) [87].

Ram extrusion is the most basic extrusion system and operates with a positive displacement ram capable of generating high pressure to push materials through the die [92]. During ram extrusion, materials are introduced into a heated cylinder and, after an induction period to soften the materials, a ram (or a piston) pressurizes the soft materials through the die and transforms them into a desired shape. The ram exerts modest and repeatable pressure as well as a very consistent extrudate diameter so this technique is suited for the precision extrusion of highly valuable materials. Whilst ram extrusion is simple and easy to use, the major drawback of this process is limited melting capacity that causes poor temperature uniformity in the extrudate [92]. Moreover, extrudates prepared by ram extrusion have lower homogeneity, in comparison with extrudates processed by screw extruders (Figure 3.5) [87].

The other extrusion systems, screw extruders, comprise a drive unit and rotating screw positioned within a heated barrel and provide more shear stress and intense mixing that ram extruders.

The single-screw extruder is the, most widely used extrusion system in the world and consists of one rotating screw positioned inside a stationary barrel. The advantage of the single-screw extrusion as a process is its mechanical simplicity and the initial reduced investments costs [92]. However, the single-screw extrusion does not provide the high mixing capability of other advanced machines and, therefore, it is not the preferred approach

for the production of pharmaceutical formulations. Moreover, dispersing and mixing of drugs with other ingredients involve breaking aggregates of minor drug particles. In order to achieve this, a critical amount of force must be applied during the process [111]. This force cannot be achieved with the single-screw, but the twin-screw would provide the high energy necessary (Figure 3.5) [109].

Twin-screw extruder are more sophisticated and involve a co-rotating or counter-rotation screw configuration and the agitation of two-screw cause high kneading potential, shorter residence time and large dispensing capacities [67, 91]. The extruder is composed of two screws aligned parallel to each other rotating in the same direction (co-rotating) or in opposite directions (counter-rotating). In the pharmaceutical industry the intermeshing co-rotation mode is preferred, since it provides intensive mixing and ensures almost complete emptying of the extruder, minimizing loss of highly valuable product [112]. Twin-screw extruders are most popular in solid dosage forms development as it imparts both dispersive and distributive mixing (Figure 3.5) [92]. In addition, the versatility of a twin-screw extruder (process manipulation and optimization) and the ability to accommodate various pharmaceutical formulation makes it more favorable for pharmaceutical industry [109]. On Table 3.2, a summary of the advantages and limitations of single-screw and twin screw extruders can be found.

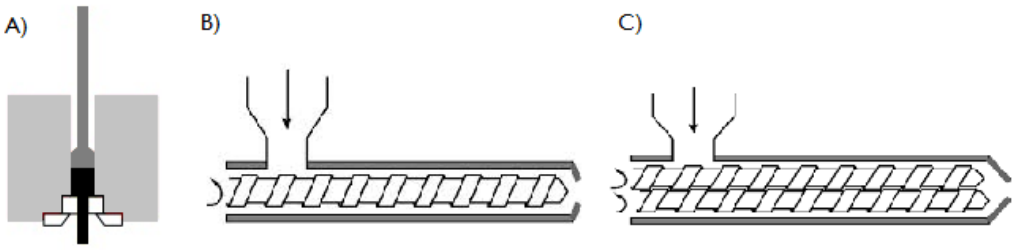
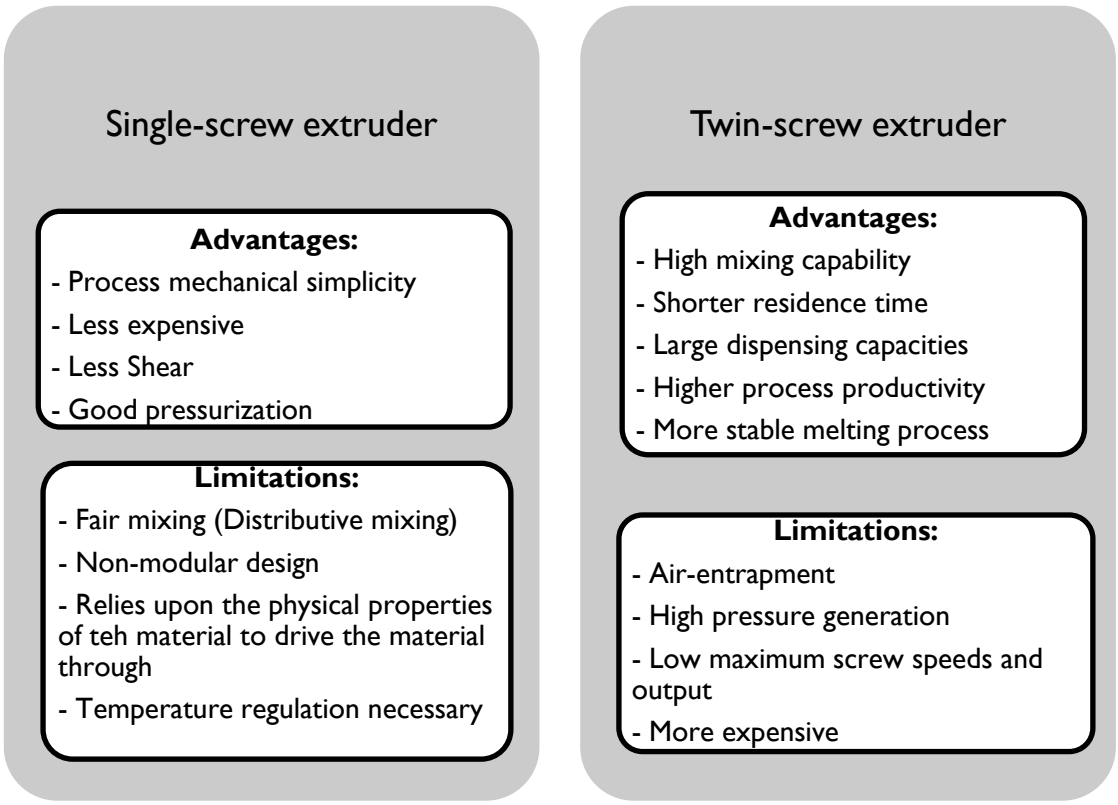


FIGURE 3.5 SCHEMATIC DIAGRAM OF EXTRUSION SYSTEMS. A) RAM EXTRUDER B) SINGLE-SCREW EXTRUDER C) TWIN-SCREW EXTRUDER (ADAPTED FROM BREITENBACH, 2012 [94]).

TABLE 3.2 ADVANTAGES AND LIMITATIONS OF SINGLE-SCREW EXTRUDER AND TWIN-SCREW EXTRUDER (ADAPTED FROM KOLTER ET AL., 2011 [101]).



In general, screw extruder consists of three distinct zones: feed zone, compression or melting zone and a metering zone; all of which exert a different pressure on the pharmaceutical powder mix. Additional systems include mass flow feeders to accurately meter materials into the feed hopper, process analytical technology to measure extrudate properties, liquid and solid side stuffers and vacuum pumps to devolatize extrudates. Single-screw extruder accepts the DS and excipients into the feed section, which has an extremely large screw flight depth and pitch. These are the perfect characteristics for consistent feeding from the hopper and gentle mixing of pharmaceutical materials [67].

At the feed zone, the pressure within the extruder is at its lowest, in order to allow for consistent feeding from the hopper and gentle mixing of DS, polymers and other excipients.

The subsequent compression zone is characterized by a gradual and progressive increase of the pressure. The increase in pressure along the length of the compression zone imparts a high degree of mixing and compression to the material. The primary function of

this zone is to melt, homogenize and compress the extrudate, to ensure the molten material reaches the final section of the barrel (metering zone) in a form appropriate for processing. [94]

After that process, the extrudate reaches the metering zone in a form suitable for extrusion. The metering zone stabilizes the effervescent flow of the matrix and ensures that the extrudate has a uniform thickness, shape and size. These properties are governed by the consistency of the melt flow and the metering zone must eliminate any pulsating flow. Consequently, a constant and steady uniform screw flight depth and pitch helps to maintain continuous high pressure ensuring a uniform delivery rate of extrudates through the extrusion die and hence a uniform extruded product [97]. Given that HME is non-ambient process involving the use of thermoplastic polymers, heat is commonly transferred to the powder mass through a combination of friction and barrels heaters (Figure 3.6) [67, 97, 113].

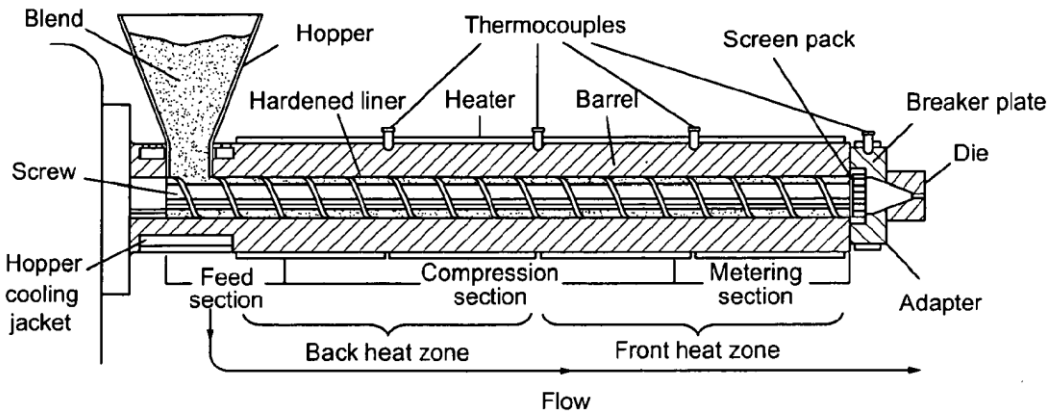


FIGURE 3.6 SCHEMATIC DIAGRAM OF A SINGLE SCREW EXTRUDER WITH REPRESENTATION OF DIFFERENTS SECTIONS (FEED ZONE, COMPRESSION ZONE AND METERING ZONE) (ADAPTED FROM POLLOCK AND GROOSMAN, 2010 [107]).

HME is a continuous process, but because only limited amounts of the DS are available at the early development stages, extrusion of smaller batch size is the preferred approach used in the pharmaceutical industries, since it ensures significant time and cost savings and allows rapid product screening and analysis. However, the scale-up of these laboratory-scale processes is essential during product development [114].

In continuous process, as HME, the scale-up is easier to achieve than the scale-up of a batch process is, since increasing the batch size only requires a longer run time using the same equipment and process parameters. Transferring the HME process from a small to

larger extruder requires characterization of the HME process to verify that the transferred process has not been altered. To confirm the precise replication of the process parameters, the following variables should be verified: melt temperature, melt viscosity, mechanical strength of the die, distribution of melt within the device and geometry of the dies [115].

3.3 Materials For Hot-Melt Extrusion

Hot-melt extrusion, as both thermal and mechanical process, applies a significant amount of heat and shear stress on the materials being subjected to this process and involves the use of thermoplastic polymeric materials as carrier systems for the DS [67]. Due to these characteristics, the drug substance and polymeric carriers may undergo chemical reactions. Therefore, selection of polymer carrier system is critical for the successful development of formulation and manufacturing processes. Hence, the chemical properties and the stability of the formulation components must be monitored in order to eliminate any degradation concerns [116].

For a pharmaceutical material to be processed by HME, it must be able to deform easily inside the extruder and solidify upon its exit. Thermal stability of the individual compounds is a prerequisite for the process although the short processing time encountered in this process may not limit all thermolabile compounds. Hot-melt extruded dosage forms are complex mixtures of active ingredient and functional excipients [87]. Polymers, plasticizers, antioxidants, lubricants and colorants are the typical hot-melt extrusion excipients and polymers and plasticizers are the most indispensable.

Polymers

The design of Hot-melt process is mostly influenced by the character of polymers; their appropriate thermoplastic characteristics are necessary for this process and high thermal conductivities and low melt viscosities are beneficial [91]. Molten or softened polymers act as binders for granulations, thus requiring no solvents. Mixing occurs thoroughly in the molten state and the drug is embedded in the polymeric matrix [117]. Polymers having Tg below the drug degradation temperatures have been widely utilized as thermal binders and retardants for melt extrusion processing [118]. The use of ionic and/or

pH dependent polymers as the carrier matrix may achieve zero-order drug release or site specific drug delivery along the gastrointestinal tract [87]. Some of the polymers which have generally been used in HME include PVP, PEO, PEG, EC, HPMC, HPC, Eudragit RSPO, Eudragit S1000 [87, 117, 118].

Plasticizers

The use of polymeric carriers usually requires the incorporation of a plasticizer into the formulation in order to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product [117]. Plasticizers are additives to polymers due their capability of lowering glass transition temperature by location between the chains of polymers, therefore plasticizers prevent chain-chain interactions significantly reducing the frictional forces between chains. Thus, polymers are softer and their structure is more flexible, improving their processability [119, 120]. Typical plasticizing agents for HME include PEGs, triacetin and citrate esters [87, 107, 121].

Other processing aids

The excessive temperatures needed to HME process may lead to polymer degradation. The stability of polymers that are susceptible to degradation can be improved with the addition of antioxidants, acid receptors and/or light absorbers. Reducing agents, such as ascorbic acid, are able to interfere with autoxidation in a preventive manner since they preferentially undergo oxidation. Chelating agents such as EDTA and citric acid are another type of preventive antioxidant that decreases the rate of free radical formation by forming a stable complex with metal ions that catalyze these reduction reactions [117].

Other materials have been used to facilitate HME processing, for example waxy material like glyceryl monostereate has been reported to function as a thermal lubricant. Vitamin E has been reported to plasticize polymers and enhance drug absorption [122].

3.4 Process Main Advantages and Limitations

HME offers several distinct advantages over traditional manufacturing techniques for pharmaceutical applications [67]. Excellent mixing and agitation during processing cause suspended drug particles to disaggregate in the molten polymer and this results in extruded formulations with good content uniformity (99%-101%) [118]. The process entails a continuous operation with fewer processing steps, less offline testing, fewer operator interventions and can be scaled up easily to improve efficiency [117].

The advantages of this technology include the increased solubility and bioavailability of water insoluble compounds; the capabilities of sustained, modified and target release; the uniform dispersion of fine particles; the good stability at changing pH and moisture levels and the reduced number of unit operations and production of a wide range of performance dosage forms [86, 97].

Other advantage is a continuous operation with a solvent-free process that does not produce residual solvents (including the possibility of recycling) and contributes for a better content uniformity in extrudates [95]. It avoids degradation problems which may be caused by the presence of residual solvents thereby resulting in improving stability for these types of compounds. As HME does not involve a granulation fluid and thus extruded materials may be cut directly into tablets or pellets avoiding subsequent compaction processes, typically required for wet- and dry-granulation techniques. Therefore, this technology allows for the rapid production of solid dosage forms while avoiding many of the current disadvantages of conventional manufacturing techniques [67].

However, this technique has also some limitations. The main drawbacks of the technique include thermal process and use of a limited number of polymers (limited number of heat stable polymers) [97]. This technique also requires raw materials with high flow properties, which is a limitation for selection of materials to be used [115]. All the components in the formulation must be thermally stable at the processing temperature utilized, which may limit the extrusion of thermosensitive actives [90]. Although this requirement may sometimes limit pharmaceutical compound from HME processing, input of new technologies, such combination of nanotechnology with powder coating, and equipment specifications have expanded the list of actives not previously thought to be applicable for this technique [87].

Table 3.3 summarizes the main advantages and limitations of HME.

TABLE 3.3 ADVANTAGES AND LIMITATIONS OF HOT-MELT EXTRUSION (ADAPTED FROM JAGTAP, P.; 2012 [109]).

Advantages	Limitations
• Enhanced bioavailability of poorly soluble compounds	• Thermal process (drug/polymer stability)
• Reduced production time, fewer steps and a continuous operation	• Flow properties of the polymer are essential to processing
• Reduced number of unit operations	• Limited number of available polymers
• Uniform dispersion of fine particles	• Requires high energy inputs
• Sustained, modified and targeted release capabilities	• The process cannot be applied to heat sensitive materials owing to the elevated temperatures involved
• Good stability at varying pH moisture levels	• Lower melting point binder could promote situations where melting point or softening of the binder occurs during handling and storage of the agglomerates
• There are no requirements on the compressibility of active ingredients and the entire process is simple and efficient	• Higher melting point binders require high melting temperatures and can contribute to instability problems (specially for heat labile material)

3.5 A VIEW TO THE FUTURE

Hot-melt extrusion technology is an increasingly attractive process for the manufacture of various drug delivery systems and has proven to be a robust method. One of the main reasons for the adoption of HME within the pharmaceutical industry is the advantages associated to increased throughput, efficient mixing and material modifications during the extrusion process. Moreover, HME is a highly versatile technology capable of producing a wide range of difference drug-delivery formulations and this technology is suitable for both high dose and potent compounds.

As stated above, pharmaceutical industrial suppliers, of both materials and equipment, have identified the importance and significance of HME as a process to further enhance drug

solubility and solid-dispersion production [92]. Undoubtedly, the major challenge is stabilizing the amorphous form of drugs. Other challenges such as drug and matrix degradation that may result from high process temperatures and shear forces can be overcome by formulation, equipment design and engineer approaches. Thus, even drugs known to be thermally labile have been processed. Indeed, research is continuing to overcome the lack of knowledge in predicting methods of increasing and enhancing drug solubility are the main issues to be tackled, whilst assessing ways to expedite the drug development process [92, 95, 97, 116].

4. Spray Drying

4 SPRAY DRYING TECHNOLOGY

The development of spray drying equipment and techniques evolved over a period of several decades from 1870s through the early 1900s. The first patent was applied in 1901 by Robert Stauf, with the intention of producing dry powders of milk, blood and other liquid solutions [123]. Although it was known and used much before, the true boom in spray drying technology was driven by the Second World War, during which a necessity for transport of huge amounts of food emerged, causing a search for new methods to reduce food's weigh and volume, as well as a search for better conservation techniques [124, 125]. During the post-war period, the application of spray drying method was also directed toward the pharmaceutical industry.

In pharmaceutical technology, spray drying is typically used as a method for removing water or other liquid from the liquid stream. It is also a very important process used for obtaining dried substances with distinct properties required for various forms of drugs [126].

The spray drying process is conceptually simple; a liquid stream is pumped through an atomizer, a plume of liquid droplets containing solid components is created and subsequently exposed to a suitable gas stream to promote rapid evaporative mass transfer of the liquid carrier into the gas. When sufficient liquid mass has been transformed to vapor, the remaining solid material present in each liquid droplet forms an individual dried particle which is then separated from the gas stream [127]. The liquid stream can be a solution, suspension, dispersion or emulsion [124].

This one-step, continuous-process has been shown to be both robust and scalable.[127]

4.1 PHARMACEUTICAL APPLICATIONS

Spray drying application in the pharmaceutical industry date to almost 50 years ago. It was first applied as an intermediate processing step in the production of solid dosage forms [128].

This emerging technology has several applications on pharmaceutical industry. In fact, since last couple of decades numerous patents were issued by the US Patent Office on spray drying technology for various applications in pharmaceutical field (Figure 4.1) [129].

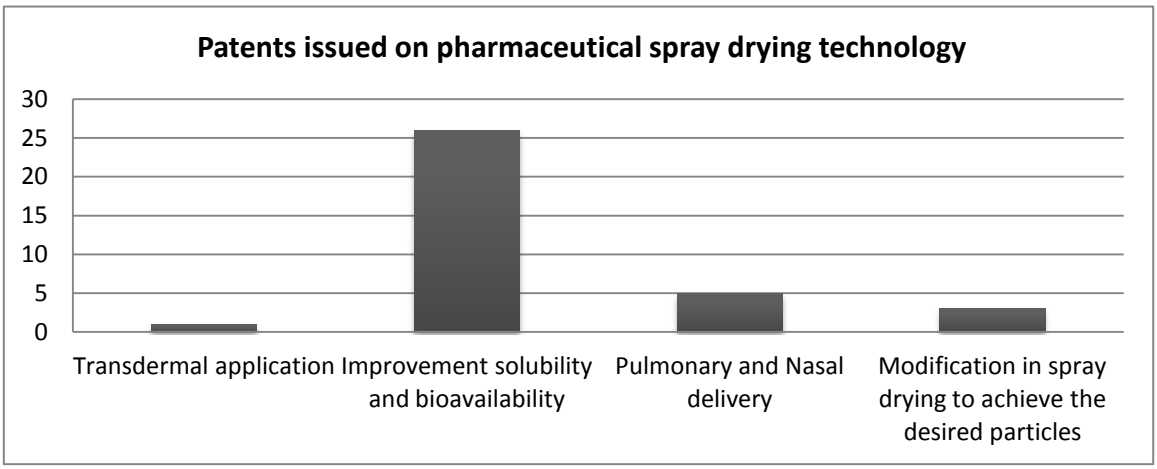


FIGURE 4.1 NUMBER OF PATENTS OF SPRAY DRYING IN PHAMACEUTICAL INDUSTRY, BY TYPE OF APPLICATION, UNTIL 2012 (ADAPTED FROM PATEL, 2014 [129]).

As explicit on Figure 4.1, it can be concluded that, nowadays, the main application of spray drying technology is the improvement of drug solubility and bioavailability. Indeed, spray drying has also extensive application in manufacturing of amorphous solid dispersion for solubility and bioavailability enhancement of various poorly soluble drugs; namely nimesulide, valsartan, celecoxib, fenofibrate, oxocarbazepine, itraconazol, alprazolam, etc.. Actually, several formulations of small molecules developed using spray drying technology are available in the market, as shown on Table 4.1.

TABLE 4.1. LIST OF SOME COMMERCIAL FORMULATION MANUFACTURED USING SPRAY DRYING TECHNOLOGY (ADAPTED FROM PATEL, 2014 [129]).

Product Brand name	Drug Substance name	Manufacturing method	Dosage form	Approval year
Progaf	Tacrolimus	Spray drying/Fluid bed	Capsule	1994
Sporanox	Itraconazole	Spray drying	Capsule	1992
Cesamet	Nabilone	Spray drying	Capsule	2006
Intelence	Etravirine	Spray drying	Tablet	2008
Nimotop	Nimodipine	Spray drying/Fluid bed	Capsule	2006

Spray Dried Powders for Inhalation

Inhalation is a pain-free and self-administrable delivery method and for these reasons it is preferred by patients and health professionals, whenever applicable [99]. The main reason for this is that although producing powders for inhalation is relatively easy on small scale, it has been hard to replicate at a commercial scale. Spray drying technology makes it easier, than ever before, to efficiently produce therapies in the form of free-flowing particles of small aerodynamic size, suitable for inhalation [130]. In addition, spray drying also offers an opportunity to incorporate high amounts of drug. Other advantages of this technology are, sustained drug delivery, targeted deposition, enhanced drug stability and absorption. The potential for creating respiratory particles by spray drying has some problems that must be addressed [126]. In fact, some limitations of using spray drying to produce aerosol particles include the fact that the yield is dependent on the formulation and that in the case of protein heat inactivation and surface denaturation are possible [129]. Also in the small molecules formulation for administration via respiratory tract there is a limitation of the inherent instability of these molecules to the higher temperature associated with spray drying process [131].

A successful drug powder inhaler product is a system which combines a stable formulation with the correct particle size distribution and a device to facilitate the delivery to the patient. Spray drying has been shown to be a scalable, robust and pharmaceutical viable process for fine powder production [132].

The first pharmaceutical product targeting systemic treatment through the pulmonary drug delivery route was inhaled insulin, Exubera, approved by the FDA on January 2006 [133].

Furthermore, successful spray drying of protein leads to the possibility of producing vaccines intended for respiratory administration. Vaccines must remain active after drying, physicochemically stable, and ready for aerosolization. It is known that it may be possible to produce active nonviral powders intended for inhalation [126, 134].

Regarding the vaccine production for respiratory delivery, spray freezing should also be mentioned as a modification of the basic spray drying process. Studies show that the influenza vaccine produced by spray freezing was appropriate for respiratory delivery and gave an even more successful immunization than the traditional intramuscular vaccine [135].

Since spray drying is a promising method for vaccine production, it is expected that the next years will be for the advance on pharmaceutical manufacturing facilities. Moreover, within the next couple of years results of early clinical trials of spray-dried vaccines should help to better clarify the suitability of the spray-drying process for vaccine production [136].

Improvement of solubility and bioavailability

Other goal of spray drying technique is to increase the solubility and, consequently, the bioavailability of some drug substances. In fact, approximately 40% of new drug substances have low solubility in water [137, 138]. Increasing the aqueous solubility of a drug substance can help in the development of new therapeutic alternatives. Moreover, approximately half of new drugs cause problems during their formulation process and fail to became marketed products due to issues related to their low aqueous solubility, low bioavailability and difficulties in administration, among others [137].

The most frequently used method for increasing the aqueous solubility of a drug is to reduce its particle size, thus increasing the surface area in contact with the solvent [126, 137]. In this context, spray drying is presented as a method to produce/create particles with reduced size and to control particle size and morphology if the material is dried from a solution. In addition, it allows for control of particle's properties [126].

Increased solubility and bioavailability using spray drying technique has been reported for several drugs, such as artemisinin [139], grizeofluvin [140], itraconazol [141], flurbiprofen [142], piroxicam [143] and nimodipine [144].

Granulation

The use of spray drying to prepare granules for subsequent processing into a dosage form is not a new concept. Indeed, spray drying has been used to form granular products with adequate particle size control (50-150 μm) from a solution or a suspension. This contrasts with traditional granulation process where a granule is formed by agglomerating dry particles through compaction or addition of agglomerating excipients [145].

Granules produced using spray drying technique are extremely consistent in terms of particle size, bulk density, and compaction behavior. These features make spray drying a suitable process for the production of directly compressible excipients such as lactose,

microcrystalline cellulose and mannitol. Spray-dried lactose is by far the most commonly encountered spray-dried excipient [146].

Excipient Production

Spray drying has also been used to produce excipients with improved performance. For example, spray dried lactose, obtained from spray drying a lactose aqueous suspension, has been used as an excipient for direct compression, for compression ready granulations, solid dispersions and more recently to manufacture dry powders for inhalation [146].

In fact, the advantage of being directly compressible is due to the more ductile amorphous lactose that is formed during drying by itself or in the presence of dicalcium phosphate [147, 148].

As stated before, also spray dried microcrystalline cellulose and mannitol has been developed and show superiority in direct compression applications to other forms [149]. Other specialty excipients such as cyclodextrins that improve drug solubility forming an inclusion complex are also spray dried into a dry solid while maintaining solubility improvements [150, 151].

Microencapsulation

Microencapsulation process involves the coating of particles or liquid droplets with a biodegradable polymer. Application of microspheres in pharmaceutical industry include controlled release, particle coating, flavor stabilization, taste masking, and physical or chemical stabilization [152].

In spray drying process, the encapsulation is achieved in one step in which desolvation and thermal cross-linking occur concurrently and the particle is coated. The fast drying process avoids significant degradation of encapsulated drugs and allows the preservation of their activity after the process [153]. Effective spray-drying coating agents have been demonstrated to coat small molecules, peptides and protein as well as non-viral gene vectors [127].

Indeed, spray drying has been shown as an effective technique to encapsulate drug substances using biodegradable polymers to sustain or modify the release of the drug substance for several applications [154].

Transdermal application

Transdermal delivery is an alternative route for drug administration because it bypass the harsh environment of gastrointestinal tract and may improve patient compliance. Unfortunately, the barrier nature of skin present difficulties for drug delivery to the target sites within the skin or into the systemic circulation through the various layers of skin [155].

Combining the micro or nanoencapsulation of spray dried particles is possible to achieve a better control of transdermal delivery [156]. Moreover the use of encapsulated spray dried drug can prolong the particles-mucosa/skin interaction, increasing the amount of drug that is absorbed [153].

For example, recently a research group had developed a melanoma cancer vaccine based in spray-dried microparticles, and showed positive results in transdermally vaccinated mice [157].

4.2 Equipment and Process Technology

The spray drying process can be described as consisting of three major events: (i) atomization of the liquid into droplets, (ii) contact of the droplets with the hot drying gas and evaporation of the solvent forming solid particles and, at least, (iii) separation of the particles from the drying gas (see Figure 4.2) [158].

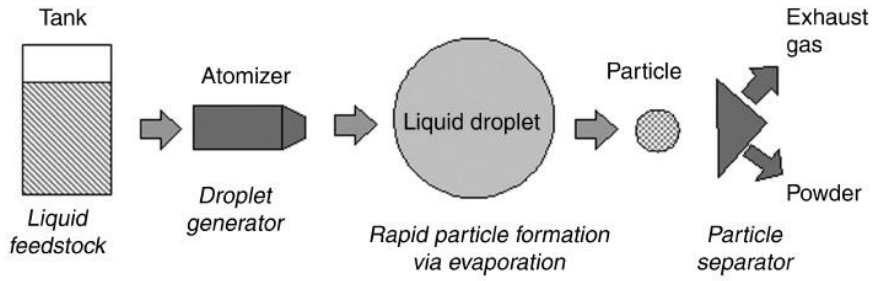


FIGURE 4.2. SCHEMATIC DIAGRAM OF SPRAY DRYING PROCESS (ADAPTED FROM SNYDER, 2008 [127]).

To support this technology, every spray dryer consists of a feed pump, an atomizer, an air heater, an air disperser, a drying chamber and systems for exhaust air cleaning and powder recovery as seen in Figure 4.3 [130].

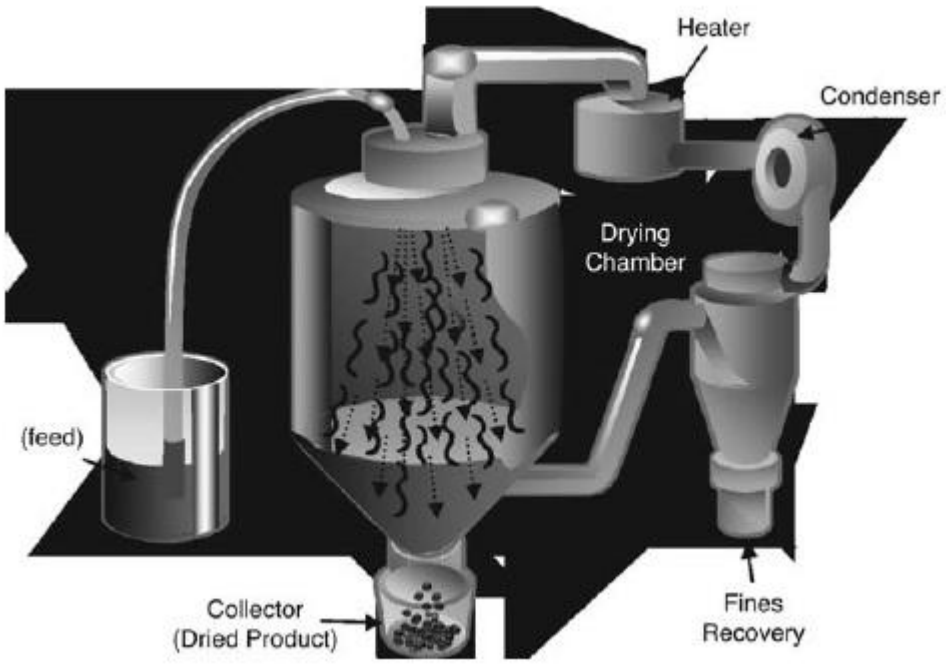


FIGURE 4.3. SCHEMATIC REPRESATION OF A GENERAL DRYING PROCESS (ADAPTED FROM PARIKH, 2009 [41]).

Atomization

Atomization is the process by which a liquid feed stock (or bulk fluid) is "atomized", or disintegrated, into droplets by means of a nozzle or rotary atomizer (see Figure 4.3). Nozzles use pressure or compressed gas to atomize the feed while rotary atomizers employ an atomizer wheel rotating at high speed. The formation of a spray with high surface/mass ratio is highly critical for optimum liquid evaporation conditions and, consequently, the desired properties and characteristics of the final dried product [99, 124].

The initial partitioning of the bulk fluid into a spray field of individual droplets is the primary factor in determining the size distribution of the final dried particles.

A key performance parameter for the atomizer is the resulting liquid droplet size distribution. Although, ideally, the sizes of all droplets should be the same, in practical terms, formation of droplets with a narrow size distribution would be satisfactory [41]. The importance of this parameter depends on the further process of spray dried particles. Controlling the droplet size distribution is essential for the consistent and efficient production of spray dried particles utilized for inhalation drug delivery in which the output is directly package into the final product form. However, if the spray dried product is an

intermediate, which is further processed (via granulation, roller compaction, tableting, etc.) tight control on droplet size may not be a major process control variable [127].

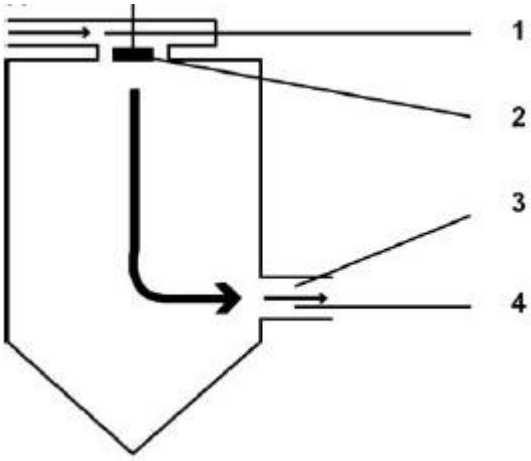
The atomization phase makes the spray drying process not only a drying method for drying heat sensitive substances (due to the reduced evaporation time), but also, more importantly, allows the formation of particles with the desired physicochemical and morphological properties [152]. These advantages will be discussed in more detail later.

Droplet-air contact

Once the bulk fluid is atomized, it must be brought into intimate contact with the heated gas to promote the evaporation equally from the surface of all droplets. This process occurs in a drying chamber, where the heated gas is introduced by an air dispenser, which ensures that the gas flows uniformly to all parts of the chamber. Air is drawn directly from the atmosphere through a system of filters and subsequently preheated [159]. It is critical that the air entering the disperser is well mixed and has no temperature gradient across the duct leading into it; otherwise, the drying will not be even within the chamber [41]. The air disperser is normally built into the roof of the drying chamber and the atomization device is placed in or adjacent to air disperser. Thus, instant and complete mixing of the heated drying gas with the atomized clouds of droplets can be achieved.

Spray drying may proceed cocurrently, countercurrently, or as a mixed-flow process [160]. Both cocurrent spray drying and mixed-flow process occur more often than countercurrent spray drying.

Cocurrent flow is the configuration in which the spray and drying air pass through the dryer in the same direction. The dried powder is released from the chamber through the outlet placed at the bottom of the chamber. The droplets fall toward the bottom of the chamber together with the airflow, simultaneously losing their liquid. This design exposes the droplets to the highest air temperature since the dispersion is released immediately into the drying air, which allows rapid evaporation results (Figure 4.4). Cocurrent dryers are used for drying substances that are relatively easy to dry and for drying at considerably high temperatures without risking over-heating of the product [125, 160].

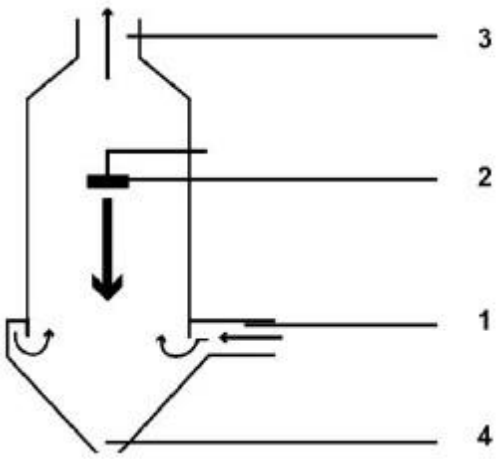


Legend:

1. Drying air inlet
2. Atomizer
3. Air outlet
4. Dried powder uptake

FIGURE 4.4. COCURRENT SPRAY DRYING PROCESS (ADAPTED FROM CAL, 2009 [117]).

In countercurrent dryers, spray and air enter at opposite ends of the dryer. The atomization of the feed occurs in the direction of the bottom of the chamber and the drying air is supplied from the bottom as shown in Figure 4.5. The droplets containing the highest amount of solvent hit the coldest air, and their drying is finished in the hottest air. The final temperature of the product is higher than the exiting air temperature. Drying in such systems produces porous powders characterized by a lower density, as well by large diameter particles; and is well suited for meeting the final spray dried properties of non-heat-sensitive materials [125, 160].

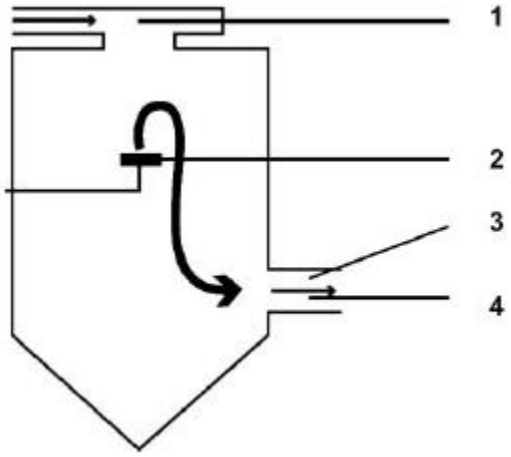


Legend:

1. Drying air inlet
2. Atomizer
3. Air outlet
4. Dried powder uptake

FIGURE 4.5. COUNTERCURRENT SPRAY DRYING PROCESS (ADAPTED FROM CAL, 2009 [117]).

As the name suggests, mixed flow is the configuration in which both co- and countercurrent flows are incorporated, which means that the feed is atomized in the direction of the upper part of the chamber, counter-current relative to the drying air (Figure 4.6). The advantage of this type of arrangement is that coarse free-flowing products can be produced in relatively small drying chambers. For thermostable substances, this is the most economical design [159].



Legend:

1. Drying air inlet
2. Atomizer
3. Air outlet
4. Dried powder uptake

FIGURE 4.6. MIXED-FLOW SPRAY DRYING PROCESS (ADAPTED FROM CAL, 2009 (117]).

Spray-air contact results in the evaporation of more than 95% of the solvents contained in the droplets in a matter of a few seconds [124] and the spray-air contact design can be selected according to the required particle size and the temperature to which the dried particle can be subjected. The balance between temperature, flow rate and droplet size controls the drying process [99].

Dried Product Collection

The completion of the particle formation process in the spray dryer creates a dispersed particulate aerosol in which the high value solid material must be separated. The particles may settle on the bottom of the chamber and be collect by appropriate devices, or they may leave the chamber together with the outgoing air. In the latter case, the separation takes place in cyclones or bag filters, while the former one requires the use of internal scraper devices [124]. The application of internal scraper device is necessary when the

drying chamber is not equipped with a cone-shapped part, or their walls convert at an angle too obtuse that do not allow the free flow of the product. These scrapers devices could be mechanical brushes, vibratory devices or a stream of compress air. However, the application of internal scraper may cause problems related to the mixing of the dried product with other parts of the feed that are not completely dried [125, 161].

The most common used separation devices, cyclones, are an industrial approach for segregating a dispersed phase from a continuous medium based upon the difference in density between phases. The concept takes advantage of the velocity lag which occurs for dense particles with respect to a lower density medium when both phases are subject to an accelerating flow field, such as within a rotating vortex [127]. The particles are then directed toward the walls of the device and are separated from the air core formed around the device's axis [125]. Cyclone separation efficiency is dependent upon the cyclone design, operating conditions, and the particle size distribution of the incoming material. The advantages of use cyclones separators included mechanical simplicity with no moving parts, high recovery efficiency and amenable to be cleaned in place [41, 125, 127].

The bag filters operate by extracting the particles from the gas stream via either a tortuous path depth or a size exclusion membrane filter. The gas phase flows though the filter while the powder forms a layer on the filter media. With the appropriate filter material and design, higher collection efficiency is possible compared with cyclone collection systems. The limitations of a bag filter are its maintenance and cleaning difficulties; if the bags ruptures will lead to loss of final dried product [127, 162].

Spray dryers in the pharmaceutical industry are available in a wide range of scales: from laboratory units where milligrams of material can be produced to very large commercial units capable of handling several tons per day [158]. One particular concern during development of pharmaceutical spray-dried products is the effect of scale-up on critical attributes. Moreover, a less careful scale-up strategy may lead to considerable losses of very expensive materials and jeopardize the timelines of a clinical program [158, 163].

4.3 Drying Gas

The principal material for pharmaceutical application of spray drying is the drying gas that will be in contact with feedstock, promoting the particle formation.

The feedstock can be prepared by suspending or dissolving the product to be spray dried in water. However, it is also common the utilization of a wide variety of organic solvents, such as ethanol, methanol and isopropanol. The solvent selection depends, frequently on the solvent characteristics and on the drug synthesis process upstream from the drying step. For example, a solvent with a low boiling point may be the only choice for a heat-sensitive material [41].

Although evaporating organic solvents by spray drying process is very efficient because of the resulting shorter time residence, as compared with water evaporation, the risk of explosion makes the use of these solvents very hazardous. A technique to solve this problem is the utilization of an inert gas as a drying gas (e.g. nitrogen) [99].

The use of nitrogen and other inert gases requires the use of a closed-cycle system for spray drying to recover the solvent and to limit the gas usage and, consequently, it is associated with higher costs including the cost of the gas itself and the cost of the installation. Nevertheless, the instability of the substance can justify the use of an inert gas [125]. Nitrogen provides the answer to the sensitivity of certain drugs to oxidation, no matter whether the feed stock is solvent or water based and, moreover, eliminates the risk of explosion posed by organic solvents [99].

4.4 Quality Control

Concerning the quality control of the spray drying process the application of PAT is currently focused on the continuous real-time quality assurance aspect. For example, in a recent study, an in-line laser diffraction system was employed for monitoring the particle sizing during the entire process [164]. This system was found to be a rapid and convenient method, which provided instantaneous information about the particle size distribution of microspheres as they are made [41]. However, this in-line system (or other real-time monitoring system) by itself does not qualify as PAT. Actually, it is crucial the judicious data management and interpretation of results from PAT-enable instruments to make valid conclusions, understanding the full process and identifying all critical sources of variability [41].

In spray drying some of the critical formulation and process factors are: material and feed properties (such as melting point of the material, feed type, solid content in the feed, additives), process variables (as feed rate, atomizer type and speed, air pressure, inlet and

outlet gas temperature) and product specifications (such as moisture content, particle size, particle density, and flow characteristics) [41, 130].

4.5 PROCESS MAIN ADVANTAGES AND LIMITATIONS

The main advantage of spray drying technique is the fact that it is a continuous process. As long as liquid feed can continue to be supplied to the drying system, the spray-dried product will continue to be produced. In some instances, this process has been operated for months. Moreover, this technique is adaptable to full automatic control [130]; once the set the points are established, all critical process parameters are kept constant throughout production and all information is fully traceable [99].

The spray drying technique is almost instantaneous as the major portion of the evaporation takes place within a few seconds. This makes spray drying well suited for heat-sensitive materials. The thermal energy in hot process gas is immediately consumed by evaporation, keeping droplet temperatures at a level where no harm is caused to product [41, 99].

Other benefit concerning the spray dryers is that they have few moving parts. In fact, with careful selection of various components it is possible to get a system having no moving parts in direct contact with the product. Operation requirements of small and large dryers are the same, which means that is relatively easy to replicate on a commercial scale [99]. This also makes spray drying a labor cost-effective process, especially for high-volume products.

At last, other advantage of spray drying is the remarkable versatility of the technology, evident when analyzing the multiple applications and the wide range of products that can be obtained. From very fine particles for pulmonary delivery to big agglomerated powders for oral dosages, spray drying offers multiple opportunities that no other single drying technology can claim [163].

However, like all other pharmaceutical processes, spray drying also has some limitations. For example, it is not well suited for producing granules with mean particle size less than 200 μm. It also has poor thermal efficiency at lower inlet temperatures and the exhaust air stream contains heat, exchange equipment removal [130].

Table 4.2 provides a resume of advantages and limitations of spray drying technology.

TABLE 4.2 ADVANTAGES AND LIMITATIONS OF SPRAY DRYING TECHNOLOGY (ADAPTED FROM MCADAMS, 2012 [136]).

Advantages	Limitations
• Continuous processing method • Equipment with few moving parts • Easy for scale-up • Remarkable versality - multiple applications • Cost-effective process	• Not well suited for producing granules with mean size >200μm • Poor thermal efficiency

4.6 A VIEW TO THE FUTURE

Spray drying is presently one of most exciting technologies for the pharmaceutical industry, being an ideal process where the end-product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density and morphology [124]. Moreover, production of dried particles from a liquid feed in a single processing step makes spray drying technology a unique and essential process.

Because of its initial inherent costs, spray drying is not always considered as a processing option for many conventional formulations, especially for small batch size operations. However, when a specialized particle type (e.g. microcapsules, controlled-release particles, nanoparticles and liposomes) is required by the active ingredient or dosage form, spray drying can become a feasible alternative to more conventional manufacturing approaches [41].

5. Liquid Dispensing Technology

5 LIQUID DISPENSING TECHNOLOGY

Many newly discovered drugs are highly potent and require an expensive engineering containment for their manipulation and the particle size is critical for having dose uniformity [165]. Although traditional methods of pharmaceutical manufacturing (such as blending, granulation, tablet compression and other techniques) show an improvement through PAT, when applied to the manufacture of lower dose and/or high potent products they have significant limitations along with the expensive scale-up.

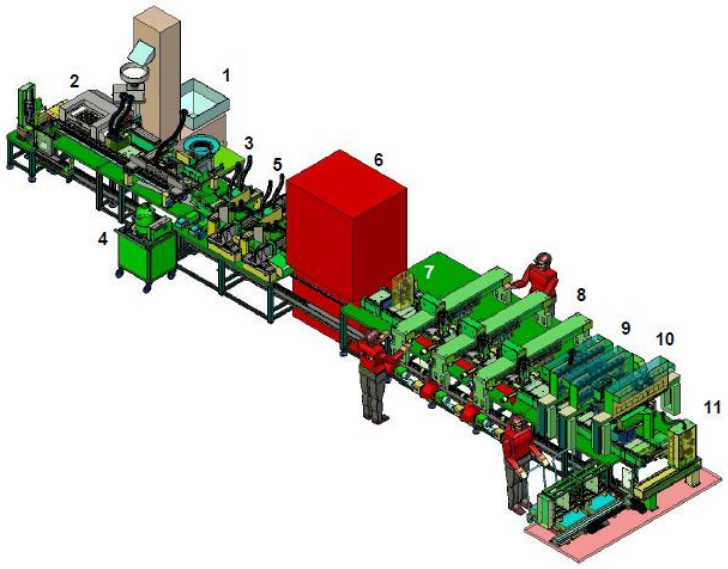
Liquid Dispensing Technology (LDT) is an innovative and revolutionary manufacturing platform technology developed by GlaxoSmithKline (GSK) to aid in the rapid development and manufacture of low-dose and/or highly potent products with an unprecedented respiratory-free environment [166]. This new dosage form provides unparalleled dose reproducibility and the process has been developed to enable real-time release. Additionally, product development can be significantly accelerated because is reduced the probability of drug-excipient interaction and consists in a scale-independent process that reduces technology transfer complexity and risk [166]. In this way, LDT can progress new products into the clinic faster, avoiding investment in the costly facilities and equipment needed to make low dose and highly potent products when compared with conventional tablet processing [165, 167].

GSK owned all intellectual property for this technology until 2008 and a GMP Pilot machine has been installed in R&D, Pennsylvania, USA since 2005. A commercial scale LDT production facility was installed at Barnard Castle in County Durham, UK in 2009 [167]. LDT was originally developed for use in immediate release products and it is suitable for doses in the range of 1 microgram to 5 milligrams. A Technology Strategy Board sponsored collaborative project that involved GSK working with Leeds and Durham Universities has significantly increased the capability of LDT, since several GSK compounds are in non-clinical and clinical development [165, 168].

The project has expanded the applicability of LDT by enabling significantly higher drug loadings and further development in the understanding of the fundamental science of the manufacturing process is necessary [165, 169].

5.1 EQUIPMENT AND PROCESS TECHNOLOGY

As stated before, this technology allows that highly potent medicines can be manufactured in a respiratory free environment within a conventional manufacturing space (Figure 5.1).



Legend:

1. Carrier tablet sorter
2. Tablet feeder
3. Carrier tablet inspection
4. Mobile vessel – API dispensing solution
5. Dispensing pumps and gantry – with wet dose position inspection
6. Drying oven/Cooling zone
7. Dried dose position inspection
8. Tablet coating and printing
9. Final tablet inspection
10. Final tablet Accept/Reject module
11. Tablet transport element inspect.

FIGURE 5.1 OVERVIEW OF LDT EQUIPMENT (ADAPTED FROM RICHARDSON. M.; WILSON, M.; 2013[160]).

The machine has a loading system, a holding system, a conveyor system, a drug dispensing system, a coating system, a printing system, a product acceptation-rejection system and a control system. Each of these systems are operably connected to each other to efficiently and ergonomically provide pharmaceutical product that is ready to packaging and which have each undergone real-time feedback and adjustment or control [170].

The final tablets are manufactured by dispensing a microlitre quantity of a liquid formulation, containing the DS, onto the surface of an inert carrier tablet. This carrier tablets are placed in a transport plate moved by a conveyor drive through the system and the dispensing of liquid formulation onto the tables is made by a precision bombing to the concave area of the carrier tablet. For higher dose of pharmaceutical product (5 or 10 mg), the DS can be dispersed on opposite sides of the carrier tablet, which allows greater volume of liquid dose. Dosing both sides of the carrier tablet would also provide the ability for

different liquid doses to be dispensed upon a single table, such as, for example, where the different liquid dose are incompatible and cannot be mixed together in liquid form [170].

In respect to dispensing and droplet volume measurement, the method involves a high precision positive displacement pump with dispense rate of 6 dispenses per second. In the next step, a calibrated imaging system captures images of droplet in flight and calculates liquid volume. The same dispenser is used in R&D and Commercial, running the same dosing solution composition at the same rate, which means that it equates to the scale-independent dispensing process. The difference between R&D and Commercial scales is that the first consists of a single dispenser and the last one consists of 4 dispensers and, thus is capable of producing up to 2 million tablets per day [171].

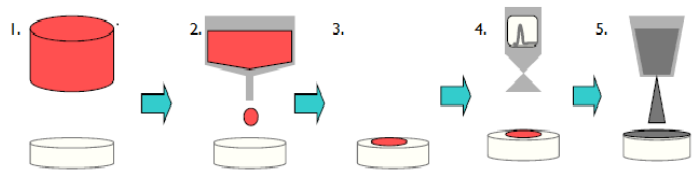
The carrier tablets preferably have reservoirs formed in both other outer surface and the opposing outer surface. Carrier tablets can also be pre-coated to prevent absorption so that the film is maintained an outer surface [170].

The dose confirmation system is operably connected to the pharmaceutical machine and determines an amount of the dosage of active agent that has been added to the pharmaceutical product. This system works with spectroscopy methods. Furthermore, the dose confirmation system can have a dose inspection system that determines a second amount of dosage of active agent that will be added to each of the carrier substrates by dispensing systems. A position of the dosage on each of the carrier substrates may be determined based on image of the droplet obtained by an incorporated camera. The NIR chemical imaging provides good penetration into the liquid dose and upper surface of the carrier tablet for an accurate measurement of the quantity of the liquid dose. This technique is especially useful for the preferred dosing step where film is positioned on the upper surface or substantially on the upper surface of carrier tablet [170].

After dispensing, the polymer present in the liquid entraps the highly potent drug substance after solvent evaporation, eliminating powdered DS from entering air and leaving adherent film polymer. An opaque, pad-printed overcoat is applied over this deposit (Figure 5.2). The opaque overcoat applied over the dried deposition by a pad printing process allows masking any color variation due to the DS and facilitates the pad printing process for marking product for commercial sale [165, 167].

It should also be highlight that carrier tablets and liquid doses can be manufactured at other facilities and delivered to LDT machine and the different properties of liquid dose (as

viscosity, for example) will determine if the resulting pharmaceutical product is an immediate release, slow release or controlled release [170].



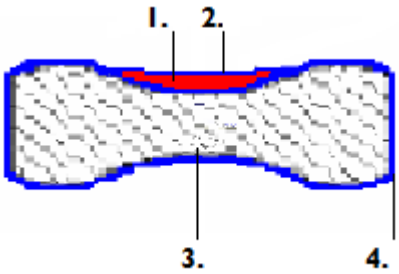
Legend:

1. Drug Solution/Suspension and Placebo
2. Liquid dispensing
3. Drying
4. On-line Imaging
5. On-line Coating and Printing

FIGURE 5.2 OVERVIEW OF LDT PROCESS (ADAPTED FROM TAINSH, D. AND PUGH, K.; 2014 [164]).

5.2 MATERIALS FOR LIQUID DISPENSING TECHNOLOGY

The tablet concept in LDT involves a biconcave carrier tablet core coated by a film. After being applied DS and polymer layer in the biconcave area, it will be overcoated by pad tamping process (Figure 5.3) [169].



Legend:

1. DS & Polymer layer
2. Overcoat applied by pad tamping process
3. Biconcave carrier tablet core
4. Carrier tablet film coat

FIGURE 5.3 COMPOSITION OF A TABLET PRODUCED BY LDT (ADAPTED FROM HILBORN, M., 2009 [159]).

Carrier tablet may be an inert carrier or may have a different DS in an immediate release (IR) or slow release (SR) matrix; usually the film coat is aqueous to prevent dosing solution "wicking" into the tablet core [167].

In the liquid DS, the solvents serve to solubilize the DS and the polymer, and are removed by evaporation during subsequent processing steps. Solvents can be, for example, methanol, ethanol, tetrahydrofuran, water. Polymers should be soluble in the solvent and form an adherent film on the tablet surface, binding the DS to the surface to facilitate droplet formation, with a well-defined shape. The polymer in formulation entraps DS after solvent evaporation eliminating powdered DS from entering air after dispensing. If solution spills, the polymer would prevent DS powder from entering environment. Another function of the polymer is the formation of large diameter droplets and no aerosol droplets [165, 167, 169]. Examples of available polymers are HPC, HPMC, carboxymethyl cellulose, polyvinyl alcohol, PVP, PEG, gelatin, acrylic copolymers or any combination thereof [170].

5.3 Quality Control

As stated before, during the different stages of tablet manufacturing by LDT there are several quality control steps, particularly in incoming core placebo tablets, dosing, drying, coating and printing [171].

In summary, the quality control inspection of incoming core placebo tablet is based on visual inspection and the dosing is ensured by wet dose position inspection, droplet weight checking, UV solution analysis, reticule calibration, droplet volume/dose content [165, 167, 169]. The drying quality is ensured by the control of tunnel temperature conditions and also by NIR dose position inspection. As for the last production step, coating and printing, a visual inspection is performed with Pad inspection and coating confirmation [165].

The LDT has on-line dose measurement of every single tablet manufactured and tablet defects are rejected automatically – the monitoring system allows tablet shift register and rejection confirmation [166].

5.4 Process Main Advantages and Limitations

LDT has significant advantages compared to conventional manufacturing methods, particularly with regard to the manufacture of low dose and/or highly potent DSs.

Some benefits of this innovative technology are unparalleled dose reproducibility and process efficiency which is due to modular flexibility, continuous processing, scale-up efficiencies (which reduces technology transfer complexity and risk – single machine process) and electronic batch record with real-time-release [165].

The process safety is characterized by reduced risk of aerosolized powder. The technology provides a shirt-sleeve environment for processing highly potent drugs, reducing the potential for operator exposure, eliminating or minimizing the need for extensive containment facilities. Indeed, the exposure levels for potent DSs are extremely low (1 $\mu g/m^3$) and LDT allow exposure levels lower than detection limits and thus the personal protective equipment (PPE) for operators is minimal. These factors were the reason for being awarded the "IChemE award" in Health and Safety category in November 2012 [167].

As LDT uses fewer excipients, this technology also minimizes the potential for instability between the drug substance and excipients and, therefore, enhances stability by reducing excipients interactions.

Another competitive advantage is that it provides an innovative dosage form where drug dissolution is independent from inert carrier tablet and that fully enables QbD through the use of PAT [166, 167].

In cost-effective terms, this technology also has some advantages including lower capital investment and lower overhead costs. Compared with high containment wet granulation facility (approximately £20 million), LDT commercial unit needs lower capital investment (approximately £7 million). With regard to lower overhead investment, LDT has smaller footprint and less safety-related expenses such as PPE purchase and maintenance, PPE training and SOPs, industrial hygiene monitoring and regulatory documentation [165, 167, 169].

5.5 A VIEW TO THE FUTURE

LDT promises to revolutionize drug product development and manufacturing with flexible and continuous process and resolve critical process safety and product quality issues with cost savings in many levels, minimizing containment requirements. This is the first intent manufacturing route for low dose/highly potent drug products in development and has already reached the clinical trials stage. At the moment, GSK is exploring collaboration with other pharma companies to exploit the technology [165, 166].

In conclusion, it should also be noted that the process inherent to LDT is protected by patent; which makes it hard the rapid dissemination of this technology by the pharmaceutical industry. Furthermore, LDT could be a differentiation factor from the other drug development companies.

6. DiffCORE Technology

6 DIFFCORE® TECHNOLOGY

The number of products based on new drug delivery systems has significantly increased in the past few years and this growth is expected to continue in the near future, with particular interest on modified release (MR) formulations [172]. Indeed, there are a number of approaches to develop a MR formulation, which include traditional polymer matrices, such as a hypromellose matrix, and more complex multilayered matrices with or without additional excipients [173-175].

DiffCORE is a new technology developed and commercialized by GSK to facilitate the rapid development of customized controlled release tablets. GSK purchased an original patent in 1993, which used a film coating based upon ethylcellulose [173]. When used in the DiffCORE process, this film coat behaves essentially as an impermeable barrier, retarding the release of the DS from the majority of the core surface area. Extended release is achieved by delivering the DS from a tablet core through one or several apertures in the impermeable coat, which maintain the release rate of the DS throughout the entire gastrointestinal tract (Figure 6.1). The combination of the properties of the tablet core, the coat and the apertures defines the drug release profile [176, 177].

FIGURE 6.1 FILM-COATED TABLES, BASED ON DIFFCORE TECHNOLOGY (ADAPTED FROM PHILIPS, D. [169])

To the best of our knowledge, Lamictal XR (lamotrigine) is the only marketed product based on this technology. Lamictal XR extended-release tablets use the DiffCORE technology in combination with an enteric coat and a polymer system that swells and erodes

to control the release rate of lamotrigine. Lamictal XR tablets are drilled on two sides of the tablet, and this modified-system is designed to delivery drug from 12 to 15 hours [173, 177].

6.1 Pharmaceutical Applications

DiffCORE is suitable for compounds with a broad range of solubility profiles, particularly for compounds with high solubility, primarily weak acids. However, weak bases form a large part of MR portfolio but were found to exhibit reduced release on leaving the gastric environment due the pH-driven reduction in solubility and thereby availability. Indeed, weak bases and salts thereof exhibit a market pH dependent solubility, i.e., they are more soluble at around pH 2, associated with regions found in the stomach, compared to their solubility in the generally neutral conditions of the small intestine, around pH 7. In order to address this problem and increase the availability of weak bases, a new film coating system was developed, enabling the use of this technology with weak bases [178]. This new coating system developed was an enteric film coat based upon previous research into different detackifiers. For the particularly cases of weak bases, the coating will retard the release of the active material to the drilled apertures while within the high solubility of gastric environment. Upon reaching the intestinal environment, characterized for higher pH, the coating dissociates and becomes soluble. This process increases the exposed area of the core, which increases the availability of the exposed drug substance, thereby compensating for the decreased solubility [173].

Further application of DiffCORE technology is the use of bilayer core, which could be an important refinement for specific compounds, depending on the products' pharmacodynamics. The combination of an IR layer and a MR layer can contribute to the improvement of the pharmacokinetic and pharmacodynamic profile of the drug; the IR layer reduces the time to reach the minimum therapeutic dose while MR layer provides a maintenance dose.

Regarding to dose ranging, products with low doses (e.g. 2 mg) have proven to be consistent and reproducible in their delivery while a high-dose product (e.g. 1000 mg) has been kept to a single daily tablet to aid patient compliance without having to use unnecessary levels of polymers [173].

6.2 EQUIPMENT AND PROCESS TECHNOLOGY

This technology is well placed with respect to the commercialization since there is a genuine need to develop modified release systems to increase patient compliance. Another aspect that has increased interest in this technology is the fact that formulations are simple to develop. The ability to manually drill apertures on low numbers of tablets or caplets allows very quick *in vitro* proof of concept, typically under week including analysis, enabling rapid development programs [173]. This approach involves creating holes of different number and size into coated tablets. The manufacture of the tablets utilizes standard manufacturing unit operation (blending, granulation and compression) till coating of tablets followed by drilling of DiffCORE apertures using proprietary drilling equipment [172]. These apertures can be produced by mechanical drilling, laser or ultrasonic cutting, and typically should correspond to 15-20% of total surface area [179].

The film coat is extremely important to this new technology since it will have influence in drug dissolution. The thickness of outer coating should be adapted such that it is substantially impermeable to the release of the drug substance during a predetermined dispensing period. Thus, a material may be suitable for use as the outer coating even if it is somehow soluble or somehow permeable to the surrounding external fluid, as long as a sufficiently thick coating is applied in such a way that the external fluid does not contact with the core except through the orifice for a sufficient period of time to allow of the release of the active agent through the orifice [180]. Furthermore, the film coat may itself contain drug substance and, consequently, be a slowed or delayed release layer. In general, the individual thickness of film coat should be between 2 and 10 microns [179, 180].

The coating may be formed by film formation from a solution or suspension spraying onto the pre-formed tablet coat. Alternatively, the tablet may be dip coated or melt coated [180].

Preferably, the coating should contain one or two orifices (apertures in the outer coat) extending from the outside of the coat [179].

As in any traditional solid dose, the manufacturing process and the core formulation can impact the performance of the final dose [173, 181].

Although there is some similarity between this MR approach and osmotic pump tablets, once they both have apertures in there coatings, the particular difference is that DiffCORE technology is based on significantly larger apertures on each face of the tablet [182, 183]. The larger apertures ensure that no hydrostatic pressures build up, and that

release is controlled by the exposed surface area, which is typical of polymer systems and not osmotic pumps [184].

TABLE 6.1 MAJOR DIFFERENCES BETWEEN OSMOTIC PUMPS AND DIFFCORE TECHNOLOGY

	Osmotic Pumps	**DiffCORE**
Aperture Sizes	Smaller	Larger
Mechanism of Drug release	Hydrostactic pressure	Exposed surface area
API release and dissolution	Risk of dose dumping	More controlled and safer

The polymer type and concentration, which dictate the erosion rate of the tablet core and subsequent diffusion rate of DS, is one of the main control mechanism associated with DiffCORE technology. Other control mechanism regards to the surface area of the core exposed for release of DS, which is controlled by the aperture size in the gastric region [173]. These control mechanisms are very advantageous since they allow reducing the risk of dose dumping and also allow the developing of a suite of release rates simply by modifying the exposed core surface area. Table 6.1 presents the comparison between the DiffCORE technfology to osmotic pumps tablets.

As shown in Figure 6.2, the i*n vitro* dissolution profile varies in function of the aperture sizes.

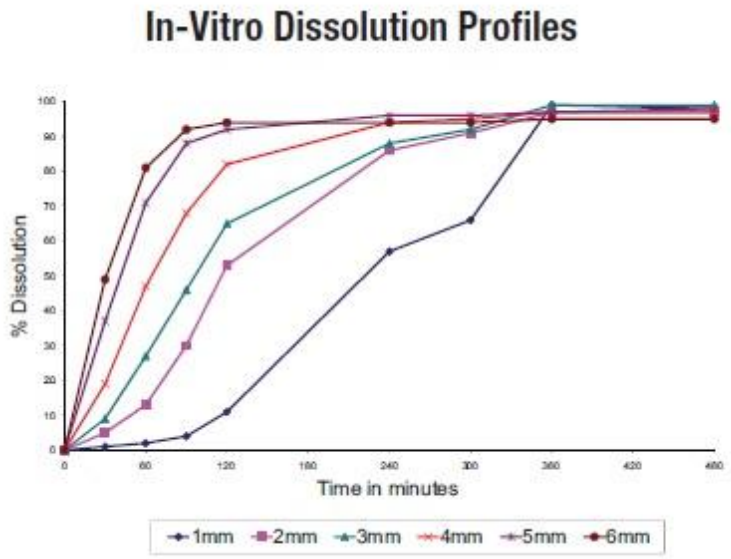


FIGURE 6.2 *IN VITRO* DISSOLUTION DATA OF A SINGLE INPUT BATCH VARYING IN APERTURE SIZES. THE DRUG WAS EXPOSED TO PH 1.2 MEDIA DURING THE FIRST TWO HOURS, FOLLOWED BY PH 6.8 MEDIA FOR THE REMAIINING SIX HOURS (ADAPTED FROM ALTRIA, K. AND TAYLOR J.;2012 [166].

Indeed, the dissolution process of the DS is controlled by two distinct mechanisms. In the first hours, the functional coating is soluble in the acidic environment of stomach and the exposed area is the dominant control mechanism and the release rate is controlled by the size apertures. The acidic environment causes the dissolution of functional coating, increasing the exposed area. Once the aperture size is large enough, the core formulation and the DS characteristics become dominant in controlling the drug release.

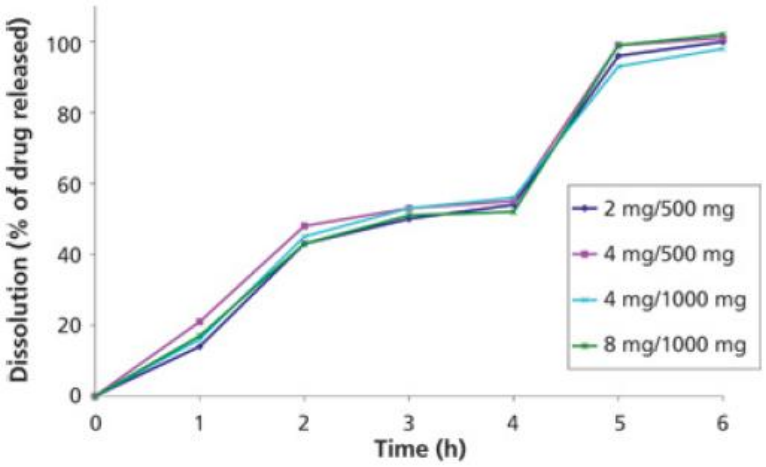


FIGURE 6.3 VARYING APERTURE SIZES ALLOWS FOR CONSISTENT PRODUCT PERFORMANCE FOR A RANGE OF DIFFERENT DOSES ON A COMBINATION PRODUCT (ADAPTED FROM ALTRIA, K. AND TAYLOR J.;2012 [166]).

The data in Figure 6.3 show a product covering four doses. Varying only the aperture sizes, doses where designed to have overlapping profiles [173].

The specific machine developed for this technology will manufacture up to 240 000 tablets per hour. Other important aspect is the on-line inspection at the point of manufacture to 100% check presence, location, size and depth of the aperture. The process is scale-independent and final development process is transferred directly to the commercial machines [173, 176].

FIGURE 6.4 COMMERCIAL MANUFACTURING EQUIPMENT WITH ONLINE INSPECTION SYSTEMS (ADAPTED FROM PHILIPS, D. [169]).

6.3 MATERIALS FOR DIFFCORE TECHNOLOGY

The tablet is usually a release-modifying system that may consist of swelling agents, osmagents, effervescent couples, eroding or degrading polymers and others.

It has already been mentioned that DiffCORE uses the combination of apertures in functional film coatings with traditional polymer matrices. The film coating may control the dissolution rate. Thus, such film coating may, for example, be composed of polymers with are either substantially or completely impermeable to water or aqueous media, or slowly erodible in water, or aqueous media or biologic liquids. Suitably the film coat should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium [179]. For that reason and unlike traditional polymer matrices, DiffCORE formulation uses a low-viscosity polymer to control

the mechanism of core erosion and diffusion. The low-viscosity polymers are more suitable because the hydration of polymer is constrained by the film coating in the gastric environment, with little erosion occurring prior to the gel-structure formulation [173]. Some examples of suitable polymers are acrylates, methacrylates, copolymers of acrylic acid or its esters and cellulose and derivates thereof (such as ethycellulose, cellulose acetate propionate, polyethylene and polyvinyl alcohol) [179].

6.4 Process Main Advantages and Limitations

As any other process, DiffCORE technology shows some advantages and some limitations.

Most of the advantages are associated with the rapid speed of developing, namely, rapid prototyping, rapid fine tuning of the drug release profile using insightful in vitro performance testing and rapid transfer to a robust commercial manufacturing process. This represents a development period often less than three months between the beginning of the project and clinical supply availability [176].

DiffCORE technology is a scale-independent process which considerably reduces technology transfer cost, complexity and risk. This technology is also characterized by the release profile typically independent of tablet strength.

Other benefit is that process optimization can be done on pilot scale validated equipment and FDA/ICH Quality by Design principles implemented from start of development. DiffCORE is, actually, a commercially used and regulatory approved technology.

Regarding to commercial manufacturing benefits, should be highlighted that DiffCORE is a robust industrial process (drilling yields typically in excess of 99.9%) with online visual inspection and GMP manufacturing facility supplying global markets.

The need for specific new equipment and an extra process during manufacturing can be a limitation to the applicability of this technology.

6.5 LAMICTAL XR ®

As referred before, Lamictal XR was the first pharmaceutical product developed with DiffCORE technology and approved to commercialization.

Before the development of Lamictal XR, the existing marketed tablet formulation lamotrigine provide immediate release of DS once the table reached the stomach. Thus, the peak plasma concentrations occurred anywhere from 1.4 to 4.8 hours following the drug administration. This represents a disadvantage because the plasma concentration (pharmacokinetic profile) achieved with the conventional tablets is cyclical, with peaks occurring after the administration followed by a pronounced decrease occurring before the next administration of drug [179].

In particular for the treatment of epilepsy it is speculated that the pronounced decrease of drug concentrations in plasma may lead to breakthrough seizures and the peak concentrations may result in some adverse events (AE).

This sustained release formulation of lamotrigine provides that substantially all the lamotrigine is release from the formulation 2 to 20 hours after administration. Administration of lamotrigine over this time period delivers it gradually to the sites where lamotrigine is readily absorbed but with a slower rise in serum concentration and reduced post-dosing peaks to mitigate dosing related AE yet provide sufficient minimum plasma/serum concentration to maintain efficacy [179].

Moreover, it is desired a release of lamotrigine in the first phase smaller than 10%. This point is extremely advantageous because it reduces the release of lamotrigine in the stomach where the lamotrigine solubility is higher, when compared to lower regions of the gastrointestinal tract. With that is possible to achieve a linear increase in plasma lamotrigine concentration and a increase on patient compliance, since it makes possible the availability of once a day tablet [179].

Regarding the materials for development of Lamictal XR, the core excipients consists of hydroxyproplyl methylcellulose K10 LV controlled-release grade, hydroxypropyl methylcellulose E4M controlled-release grade, lactose monohydrate and magnesium stereate. The tablet core running powder is prepared by wet granulation. The impermeable membrane is prepared from a film coat of Eudragit L30 D-55 that controls the release of the drug in the stomach. The matrix methylcellulose polymer retards release by a swelling and erosion mechanism [177].

6.6 A VIEW TO THE FUTURE

Due to the nature of this technology, there has been a perceived level of risk associated with "being the first" so the initial uptake has been with a compound which presented a number of challenges or difficulties in developing a more traditional MR dose form. Nowadays, GSK is using DiffCORE technology in an increasing number of products for treatment of different disorders, namely metabolic disorders, which is the case of a metformin formulation [185]. The names of the other products that are being developed using this technology have not been announced by GSK yet.

A small investment in targeted work can lead to advances that benefit the business as well as the patient, provided that the relevant risk/benefits are monitored at all stages of the process.

Future research will study the use of bilayer approach in combination products, to further modify release or deliver multiple compounds from a single tablet [173].

7. Conclusion

7 CONCLUSION

Currently, the pharmaceutical industry is facing a paradigm shift. More complex drugs, impatient regulators and increased market pressures leave little doubt that manufacturing will no longer be viewed as a standalone activity, but will be considered, along with research, clinical trials and marketing, as a very important part of the business strategy of the companies.

This monograph highlights the urgent need of innovative technological solutions that characterized the pharmaceutical manufacturing sector. The big challenge is the recognition of the need to move away from the status quo, to accept that there may be some risks in making those changes and be willing to accept those risks.

Effective manufacturing process can reduce manufacturing costs, and this itself can be a significant competitive advantage. Furthermore, effective and efficient process development contributes more towards a company's ability to accelerate time to market, ramp up production rapidly, enhance customer acceptance of new products and develop a stronger proprietary position. Moreover, the adoption of approaches such as continuous processing, implementation of Quality-by-Design and Process Analytical Technologies are encouraged by the regulators because it contributes for more efficient process. With this in mind, most of described methodologies included these approaches.

Indeed, the presented pharmaceutical manufacturing technologies in this monograph provide an opportunity for innovation and improvement since they provide a creative link between engineering and pharmaceutical sciences for the purposes of drug delivery.

Additionally, the non conventional manufacturing processes referred have several pharmaceutical applications to circumvent some issues as lower drug bioavailability, high potent drugs, and targeted drug delivery systems, among others. Of the presented technologies, three of them (HME, Spray Drying and DiffCORE) are actually applicable at industrial scale, with marketed drug products. The remaining techniques are not yet widespread but they have proven to have added value to the pharmaceutical manufacturing sector.

Regardless of the outcome, it is clear that manufacturing will assume as an important differentiator factor in pharmaceutical industry, providing several opportunities of growth and optimization.

In summary, the elements required for production of high-tech future pharmaceuticals have been developed, gaps have been identified and it is very important to continue the joint effort between academy, industry and regulatory experts.

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