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Michael A. Repka
Nigel Langley
James DiNunzio *Editors*

Melt Extrusion

Materials, Technology and Drug Product Design

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. . . To My wife Staci, for her unwavering devotion, and love for our family.
My mother, for leading her children into intellectual pursuits. My father, for his unselfish support and guidance. My brother, for his uncompromising principles and loyalty. My children, Michael, Jonathan, Andrew, Jordyn, and Walker, for making everything worthwhile.

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Nigel Langley

Preface

In the quest to develop new and better therapies to improve the quality of patients' lives, the pharmaceutical industry has relied on a combination of internal innovation and adaptation of external technologies to progress molecules to medicines. Today, melt extrusion stands as one of the several significant adaptations that have enabled therapies and produced novel drug products. The technology currently supports over a dozen commercial products and a range of novel compounds are currently in development using extrusion.

Having a lineage dating back to Archimedes, the concept of extrusion has progressed significantly over the centuries. The first modern designs for the twin screw extruder date back to the 1930s and with the development of the Erdmenger designs to achieve intermeshing and self-wiping in the 1950s, the technology has demonstrated utility and versatility. As an industrial process, the technology has supported a range of products, covering everything from space shuttle components to trash bags and wine corks. Serving as a low-cost production platform, the technology has penetrated a number of fields. Most recently, the technology has gained significant traction in the pharmaceutical space. Surprisingly to many, the technology traces its history back more than 30 years to the approval of Lacrisert, the first melt-extruded pharmaceutical product launched by Merck in 1981. Other major milestone products in the pharmaceutical space manufactured with hot-melt extrusion have included Rezulin, Kaletra, Nuvaring, and Ozerdex. Today, the technology is poised for an explosion as pharmaceutical applications extend into continuous processing, controlled release, and advance drug delivery devices.

It is also not surprising that interest in melt extrusion and the continued interest in solid dispersion technology has been supplemented by a wealth of publications. Within this space, *Melt Extrusion: Materials, Technology and Drug Product Design* has been developed to provide a definitive source on melt extrusion technology in the pharmaceutical arena. This text covers the history of and current technology for hot-melt extrusion. It also provides unique insight from excipient developers whose materials provide the basis for the production of solid dispersion products prepared using hot-melt extrusion. Fundamental overviews of formulation design and characterization are also presented and supplemented with unique industrial perspectives on modern applications of pharmaceutical hot-melt extrusion. The different viewpoints

expressed by the authors and their respective organizations highlights the versatility of extrusion technology and points to the future path of the technology within the industry. As editors we wish to acknowledge and thank the authors, for without their contributions and valuable insight this text could not have been possible. It is through their collective efforts that such a comprehensive and valuable text was created and it is hoped that this text will aid in the continued growth of pharmaceutical hot-melt extrusion.

Dr. Michael A. Repka
Dr. Nigel Langley
Dr. James DiNunzio

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Part I
Introduction and Equipment

Chapter 1
Melt Extrusion in Drug Delivery: Three Decades of Progress

Sejal Shah and Michael A. Repka

Abstract This chapter appraises the role of melt extrusion as a solubilization and bioavailability enhancement technique. The introductory chapter highlights major aspects of hot melt extrusion (HME) technology as applied in the pharmaceutical industry, particularly processing techniques, material considerations, recent innovative applications of melt extrusion in drug delivery system design, and a review of current HME-based formulations (marketed or under commercial development). The chapter also focuses on key development aspects of HME processes, such as material sparing screening approaches, process formulation relationships, and stability evaluation of prototype formulations, which emphasize the clinical and biological significance of this technique. In addition, it displays the journey and evolution of this important processing technology into an established pharmaceutical manufacturing platform. The chapter describes several case studies wherein melt extrusion has been utilized to develop commercial drug products.

1.1 Introduction

Although hot melt extrusion (HME) has been a workhorse technology in the plastics industry since the 1930s, research and development within the pharmaceutical manufacturing industry over the past two decades has propelled HME as an alternative "platform technology" for solid dosage form development. Over recent years, several studies have been published describing the use of HME as a technique of choice to address the formulation challenges of new drug molecules. Moreover, several aspects of HME have been extensively reviewed time and again (Breitenbach 2002; Crowley et al. 2007; Repka et al. 2007, 2008, 2012; Shah et al. 2013). Additionally,

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the total number of HME-based patents (in comparison to patents granted for other formulation development techniques) has been on a steady rise worldwide.

This introductory chapter highlights major aspects of HME technology as applied in the pharmaceutical industry, particularly HME processing techniques, material considerations, recent innovative applications of HME in drug delivery system design, and a review of current HME-based formulations (marketed or under commercial development). Furthermore, the chapter introduces some of the important topics discussed in the subsequent chapters in this textbook and provides a perspective on the future of this important technique in the pharmaceutical scenario.

1.2 HME as a Drug Delivery Technology

In the HME process, the drug becomes embedded in a carrier system, usually consisting of one or more thermoplastic polymers (Prodduturi et al. 2007; Özgüney et al. 2009; Ghalanbor et al. 2010; Schilling et al. 2010b), low-melting waxes (Liu et al. 2001), sugar alcohols (Ndindayino et al. 2002a), or starch (Bialleck and Rein 2011) . Molten polymers or waxes function as thermal binders during the extrusion process and upon cooling and solidification, act as drug depots and/or drug release retardants. Additionally, functional excipients, such as plasticizers (Repka et al. 1999; Crowley et al. 2002; Wu and McGinity 2003; Crowley et al. 2004; Verreck et al. 2006; Schilling et al. 2007; Thumma et al. 2008a; Schilling et al. 2010a), diluents (De Brabander et al. 2000; Özgüney et al. 2009), pH and release modifiers (Verhoeven et al. 2006; Schilling et al. 2008), stabilizers (Thumma et al. 2008b), surfactants (Ghebremeskel et al. 2006; Thumma et al. 2008b), antioxidants (Crowley et al. 2002; Wu and McGinity 2003), and processing aids (Zhou et al. 1996; Liu et al. 2001) can also be incorporated in the HME process to enhance its efficiency and overcome process limitations on a case-by-case basis.

HME offers some distinct advantages over traditional pharmaceutical formulation techniques. Namely, it is a solvent-free technique, entails a continuous operation (necessitating fewer processing steps), does not require major downstream processing such as compression, and is known to improve bioavailability due to molecular dispersion of the drug in the final dosage form (Forster et al. 2001; Ndindayino et al. 2002; Breitenbach and Magerlein 2003). High processing temperatures, however, tend to limit the applicability of HME in processing thermolabile compounds. However, the combination of HME with other technologies, such as nanotechnology (Miller et al. 2007), powder coating (Sauer et al. 2007) and complexation (e.g., cyclodextrins) (Fukuda et al. 2008; Upadhye et al. 2010) has demonstrated the versatility and inclusiveness of HME.

The end result of HME technology has been a wide array of pharmaceutical dosage forms, such as pellets (Bialleck and Rein 2011) , granules (Liu et al. 2001), immediate and modified release tablets (Crowley et al. 2002; Gryczke et al. 2011), oral fast dissolving systems (Gryczke et al. 2011), transdermal (Repka et al. 1999; Repka and McGinity 2001), transmucosal delivery systems, transungual delivery systems

Table 1.1 Currently marketed and developed drug products produced utilizing hot melt extrusion (HME) technology. (Adapted with permissions from DiNunzio (2012))

Product	Indication	HME purpose	Company
Lacrisert® (Opthalmic Insert)	Dry eye syndrome	Shaped system	Merck
Zoladex™ (Goserelin Acetate Injectable Implant)	Prostate cancer	Shaped system	AstraZeneca
Implanon® (Etonogestrel Implant)	Contraceptive	Shaped system	Organon
Gris-PEG (Griseofulvin)	Antifungal	Crystalline dispersion	Pedinol Pharmacal Inc.
NuvaRing® (Etonogestrel, Ethinyl Estradiol depot system)	Contraceptive	Shaped system	Merck
Norvir® (Ritonavir)	Antiviral (HIV)	Amorphous dispersion	Abbott Laboratories
Kaletra® (Ritonavir/Lopinavir)	Antiviral (HIV)	Amorphous dispersion	Abbott Laboratories
Eucreas® (Vildagliptin/ Metformin HCl)	Diabetes	Melt granulation	Novartis
Zithromax® (Azythromycin enteric-coated multiparticulates)	Antibiotic	Melt congeal	Pfizer
Orzurdex® (Dexamethasone Implantable Device)	Macular edema	Shaped system	Allergan
Fenoglide™ (Fenofibrate)	Dyslipidemia	MeltDose® (Solid dispersion)	Life cycle Pharma
Anacetrapib (Under Development)	Atherosclerosis	Amorphous dispersion	Merck
Posaconazole (Under Development)	Antifungal	Amorphous dispersion	Merck

(Mididoddi et al. 2006; Mididoddi and Repka 2007), and implants (Ghalanbor et al. 2010).

In addition to the versatility (array of dosage forms), this technology offers several advantages in terms of varied application, such as bioavailability enhancement, controlled release, taste-masking, abuse deterrent (Bartholomaeus et al. 2012), and shaped delivery (direct shaping, powder, granules, spheres, films, and patches). Moreover, being a continuous process it has advantages of high throughput, online monitoring, less processing, and minimal process variables.

To date, there are several commercial pharmaceutical products in development using melt extrusion technology (Table 1.1; DiNunzio 2012) demonstrating the production and scale-up feasibility of melt extrusion. In addition, melt extrusion is also developing as an alternative formulation process for drugs in clinical trials.

1.3 Development of Hot Melt Extruded Products

Over the years, melt extrusion has seen a subtle transition from being a novel formulation technique to an essential platform technology in the drug development process. This paradigm shift is due to an overwhelming number of lipophilic drugs entering the development cycle. Melt extrusion finds two distinct roles in the drug development process. The first being solubility and bioavailability enhancement of new molecular entities and risk mitigation strategies for BCS class II drugs and second by life cycle management (LCM) of already commercialized drug products.

LCM is a successfully adopted, innovative, and preemptive strategy to help sustain the market share against strong competition from generic manufacturers or superior products in development. Most companies resort to reformulation or formulation changes as an alternative LCM strategy for blockbuster molecules. LCM through reformulation or by developing enhanced drug delivery systems encompasses a spectrum of innovative delivery technologies, not limited to modified-release for oral delivery, taste-masking, orally disintegrating tablets (ODTs), depot formulations, high-strength parenteral, inhalation, emerging technologies for bioavailability enhancement (melt extrusion, spray drying, and other solubilization techniques) as well as others. An inherent advantage of this approach leads to improvement in the product's therapeutic benefits, and patient's convenience, as well as compliance, thereby extending a product's profitable life. However, for the purpose of this chapter we would discuss melt extrusion as an independent formulation development strategy as applied in early- and late-stage pharmaceutical product development processes.

1.3.1 Early-stage Development

Early-stage development in melt extrusion encompasses various critically interdependent areas involving process considerations, stability assessment of prototype formulations, and performance evaluation (with respect to intended applications) of prototype formulations.

1.3.1.1 Processing Considerations

Processing considerations is a rather broad terminology covering material properties, instrument considerations, and process-formulation interplay. Systematic research over the last couple of decades has revealed that critical product quality attributes are directly dependent on both "formulation" and the "process" employed. It is important to note that the interplay between these determines the finished product attributes.

Material Properties

All of the materials used in melt extrusion (drugs, carriers, processing aids, release modifiers, etc.) should meet certain minimal pharmaceutical criteria, which

includes well-characterized safety, and toxicological properties. Thermal stability of the individual components is a prerequisite for the extrusion process, although the short processing times encountered in HME also permit its applicability to thermolabile compounds. The incorporation of plasticizers may lower the processing temperatures encountered in HME, thus reducing the drug and carrier degradation. Incorporating various release-modifying agents can also modulate drug release from extruded systems.

Besides these, the active pharmaceutical ingredient (API) and carrier-related physicochemical properties such as melting point (T_m), glass transition temperature (T_g), melt viscosity, molecular weight, ionic nature, partition coefficient, chemical structure, stability and solubility (pH dependent if any), solubility parameters, number and type of hydrogen bond accepting or donating groups, physical state, hygroscopicity, lipophilicity, and others are key preformulation parameters. The API-related physicochemical properties as determined during preformulation studies guide the preliminary selection of carriers. Carriers are broadly classified as polymeric or nonpolymeric and its selection is based on the intended application. Table 1.2 provides a comprehensive list of carriers used in melt extrusion and its corresponding T_g and T_m values (Repka et al. 2012). The bottlenecks in employing melt extrusion as a processing technology are predominantly, very high-melting temperature of the API, thermal instability of drug and polymer, and high melt viscosity of the drug-polymer mixture. Hence, depending on the nature of the problem encountered, the development strategy is appropriately modified to be amenable to the melt extrusion process.

Screening Criteria and Selection

The pursuit to develop a melt extrusion-based prototype formulation, wherein the intended application is solubilization of the already identified drug-polymer combinations, can be further narrowed down by applying miniaturized (material sparing) screening methods. Such methods determine the drug-polymer miscibility or solubility and stability and employ a screening method coupled with a medium throughput analytical characterization tool. The screening method consists of films, quench cooled melts, and drug-excipient blend whereas the analytical tools generally consist of microscopy, spectroscopy, and calorimetric methods. A collective assessment of these miniaturized-screening experiments would assist in selecting the prototype drug-polymer combinations and drug loads at which the system is stable. Dai et al. (2008) present a comprehensive overview of the screening assays to rapidly identify solubility-enhancing formulations (Dai et al. 2008). Their review addresses three important facets of screening assays high-throughput nature (96 well formats), miniaturization (material sparing; small sample size), and automation (minimal manual intervention).

Barillaro et al. (2008) describe a high-throughput approach for evaluation of phenytoin solid dispersion. Their approach utilized automated solvent casting and subsequent dissolution testing as a screening method (Barillaro et al.

Table 1.2 Carriers used to prepare hot melt extruded dosage forms. (Adapted with permissions from Repka et al. (2012))

Chemical name	Trade name	T_g (°C)	T_m (°C)
Ammonio methacrylate copolymer	Eudragit® RS/RL	64	–
Poly(dimethyl-aminoethylmethacrylate-co-methacrylic esters)	Eudragit® E	50	–
Poly(methacrylic acid-co-methyl methacrylate) 1:2	Eudragit® S/L	160	–
Cellulose acetate phthalate	–	165	192
Poly(vinyl pyrrolidone)	Kollidon®	90–156	–
Poly(vinyl acetate)	Sentry® plus	35–40	–
Hydroxypropyl methylcellulose phthalate	–	137	150
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64	101	–
Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer	Soluplus®	70	–
Hydroxypropyl methylcellulose	Methocel®, Benecel®	160–210	–
Hydroxypropyl methylcellulose acetate succinate	Aqoat-AS®	~ 120	–
Ethyl cellulose	Ethocel® Aqualon® EC	130–133	
Hydroxypropyl cellulose	Klucel®	Softens at 130 °C	Chars at 260–275 °C
Polyethylene glycol	Carbowax®	–17ºC for MW 6000	37–63ºC
Polyethylene oxide	PolyOx® WSR	–57 to –50 °C	62–67 °C
Polymethacrylates	Eudragit ® RSPM Eudragit ® E	52, 40 °C	–
Carnuba wax	–		81–86 °C
Glyceryl palmitostearate	Precirol ATO 5®	–	52–55 °C
Glyceryl trimyristate	Dynasan 114®	–	55–58 °C
Triglyceride tripalmitin	Dynasan 116®	–	61–65 °C

MW molecular weight

2008). Mansky et al. (2007) have extensively described screening methods addressing drug-polymer combinations particularly solubility-enhancing applications (Dai et al. 2007; Shanbhag et al. 2008). Figure 1.1 illustrates the process flow of one such screening method, describing the strategy to determine ideal drug-polymer combinations displaying improved drug solubilization.

One of the major limitations of the above-mentioned screening methods is lack of consistent predictability at a large scale, i.e., findings of such high-throughput screening methods may not hold essentially true for large-scale processing methods

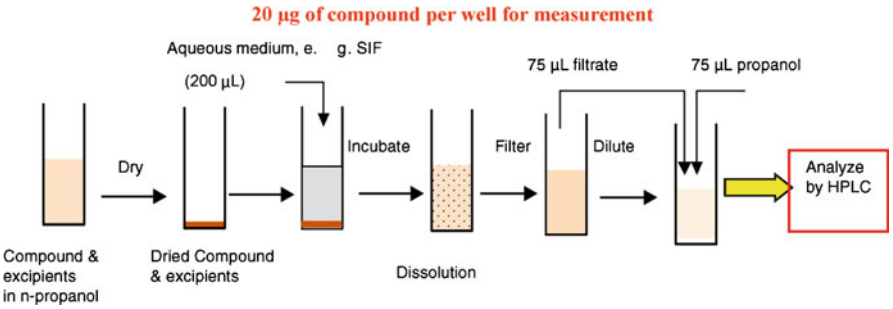


Fig. 1.1 Schematic diagram illustrating formulation screening process workflow. (Adapted with permission from Dai et al. (2007))

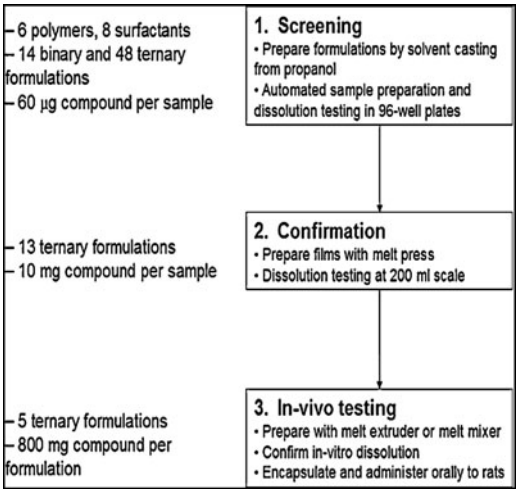


Fig. 1.2 Schematic illustration of the different stages of experimentation. At each subsequent stage, fewer samples are examined; the samples are larger and more compound is used per sample; and the formulation preparation and characterization methods become more relevant to traditional-scale formulation development work. (Adapted with permission from reference Shanbhag et al. (2008))

such as spray drying or melt extrusion. Shanbhag et al. (2008) developed a modified screening method for evaluating drug or polymer solid dispersion formulations. The method employs melt press as an additional "confirmatory step" to identify "hits," which is amenable to melt extrusion as a scale-up processing method (Fig. 1.2).

The authors evaluate the predictive value of the solvent casting-based screening method by selecting 13 hits from the screening stage, further processing them by melt press and testing the dissolution *in vitro*. The screening method successfully identified formulations, which upon melt processing (by melt press), demonstrated better dissolution profiles (Fig. 1.3).

Subsequently, five hits from the melt processing stage were selected for processing at a larger scale by melt extrusion. The oral bioavailability of all five formulations (hits) as evaluated in rats, exceeded that of the unformulated compound by a factor of about 20 (Fig. 1.4).

Polymer \ Surfactant	None	SLS	Poloxamer 407	Crodesta F110	Crodesta F160	Tween 80	Vitamin E TPGS	Volpo 10	Cremophor EL
None	0	0	1	8	31	56	85	87	89
Eudragit RS100	0	5	1	0	0	3	1	3	13
Kollidon VA 64	0	**48**	21	31	**70**	32	**52**	64	18
Plasdone K29/32	0	17	20	14	**59**	72	**56**	66	**79**
HPC SL	4	65	0	22	**36**	4	**54**	44	17
Eudragit L100	17	4	**59**	40	**56**	50	**59**	62	**70**
HPMCP 50	20	5	1	18	39	8	**43**	64	38

Fig. 1.3 Summary of the results of the screening experiments.The number in each cell is the average value of % dissolved after 1 h of incubation in SIF ($n = 3$ or 6). The color of the cells indicates whether % dissolved was < 25 % (*orange*), between 25 and 50 % (*yellow*), or > 50 % (*green*). The *top* row contains the results for surfactant-only formulations; the *left* column contains the results for polymer-only formulations; the *upper left* corner contains the results for the unformulated compound (no excipients), which was processed by solvent casting in an otherwise identical manner to the formulations; and the remaining cells contain the results for polymer or surfactant formulations. The 13 formulations that were scaled up using the melt press method are identified by the use of a *bold* or *underlined* font (e.g., 79) for % dissolved. (Adapted with permission from reference Shanbhaget al. (2008))

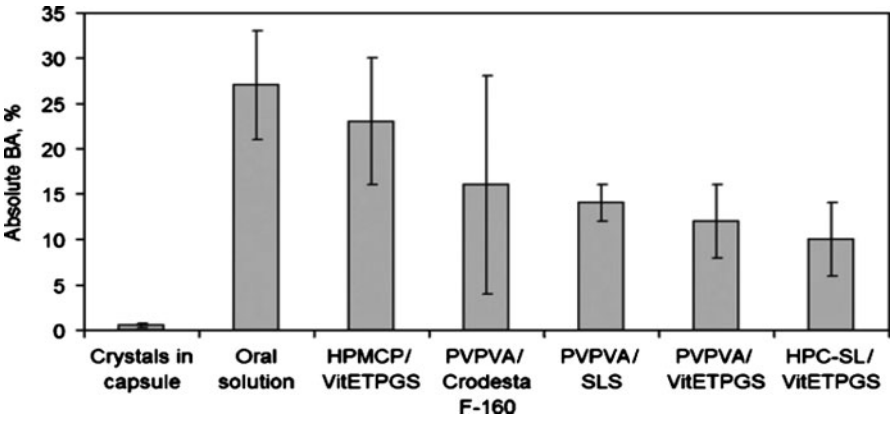


Fig. 1.4 Oral bioavailability of different formulations in rats ($n = 6$). (Adapted with permission from reference Shanbhag et al. (2008))

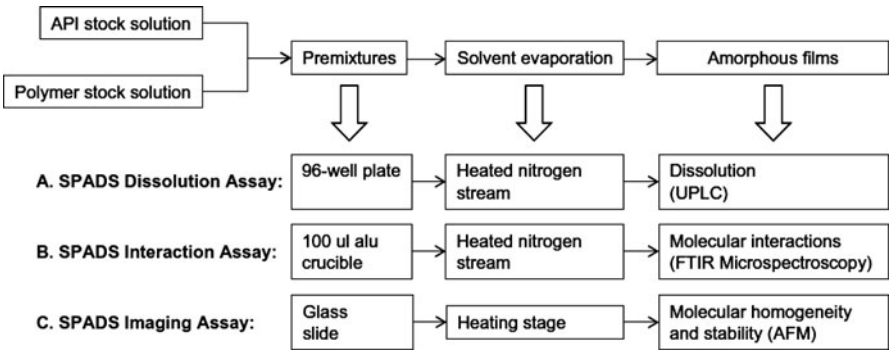


Fig. 1.5 Schematic representation of the experimental procedure of the different SPADS assays. (Adapted with permission from reference Wyttenbach et al. (2013))

While the earlier-described approaches focus on the assessment of the supersaturation potential of the polymer, there are some methods describing the evaluation of amorphous drug stabilization in the solid state (van Eerdenbrugh and Taylor 2010; Lauer et al. 2011; Weuts et al. 2011).

Wyttenbach et al. (2013) present an interesting strategy to identify amorphous solid dispersions (ASD) with maximum supersaturation and solid-state stability. The authors employed three different miniaturized assays (SPADS dissolution assay, FTIR microspectroscopy-based SPADS interaction assay, and atomic force microscopy-based SPADS imaging assay), combined in a two-step experimental flow to determine both the supersaturation potential and the stability of amorphous compositions thus formed with different drug-polymer combinations (Fig. 1.5; Wyttenbach et al. 2013).

The next step in the early-stage development is to extrude different preselected compositions by using scaled-down material-sparing extruders. This step would confirm its extrusion processability and determine the further need of processing aids, etc, which ultimately leads to a prototype formulation.

Stability Evaluation of Prototype Formulation

Stability is assessed during screening, and it is imperative to evaluate physical and chemical stability at all stages of development . The stability of developed melt extruded prototype formulations is assessed by following standard protocols and industry practice.

Stability evaluation is very critical particularly in the case of less stable ASD, at times resulting in the recrystallization of drug from solid dispersions during the manufacturing process, and subsequently during storage (Vasconcelos et al. 2007). The solubility and miscibility of drug in the polymer is directly related to the stabilization of an amorphous drug against crystallization (Qian et al. 2010).

Physical stability of ASD could be improved by the antiplasticization effect of polymers (increasing the viscosity of the binary system and decreasing the diffusion of drug molecules) that would raise the glass transition temperature of the system (Van den Mooter et al. 2001; Kakumanu and Bansal 2002; Sathigari et al. 2012). Hydrogen bonding and hydrophobic interactions between the drug and polymer are the primary driving forces for the formation of solid dispersions during melt extrusion, inhibition of drug crystallization during subsequent storage of melt exudates, and achievement and sustainment of supersaturation in the GI tract.

Storage temperature (Taylor and Zografi 1997; Matsumoto and Zografi 1999; Khougaz and Clas 2000; Miyazaki et al. 2004; Konno and Taylor 2006) and presence of moisture (inherent, during processing or storage) (Rumondor et al. 2009; Marsac et al. 2010) is an important factor resulting in recrystallization and amorphous-amorphous phase separation (Rumondor et al. 2011). The primary packaging component also needs to be properly designed to minimize the water permeation. Thorough characterization of the physicochemical properties of ASD and their corresponding *in vivo* behavior is required for the rational application of these systems in the pharmaceutical industry.

1.3.1.2 Instrument Considerations

Pharmaceutical melt extruders are specifically configured to meet current regulatory norms of manufacturing dosage forms. Extruders are available as single (smooth or grooved barrel), twin (corotating or counter rotating with intermeshing or nonintermeshing types), or multiscrew extruders (static or rotating central shaft). Single screw extruders (SSE) essentially consist of a one-piece screw, which continuously rotates within a barrel developing a good quality melt and generates enough pressures for extrusion. Relatively simple engineering design, combined with low cost and maintenance, make it the machine of choice for the production of virtually all extruded products. On the other hand, it faces limitations of high-pressure compression of dispersed particulates during melting, which leads to agglomerate formation and then insufficient shear deformation further results in poor mixing characteristics.

However, recently, Costeux et al. (2011) proved in 2011 that the SSE could have dominant elongational flow where melting occurred before compression by incorporating a series of spiral flow elongational mixers (SFEM) on to the screw. Due to its elongationally dominant feature, it breaks down blends of high viscosity ratios that cannot be dispersed by shear alone, hence, obviating the need to break the agglomerates. Unlike the twin-screw extruders (TSEs), all of the material can consistently pass through the elongational mixers thereby embedding single heat history. Melting and mixing mostly occurs near the hopper so that a significant part of the total length of the SSE plays a role of mixer. TSEs have overtaken SSEs in pharmaceutical processing and have become the dominant continuous compounding mixer for drug-polymer blends. The TSE works on a fundamentally different and superior principle that is not shear dominated. It melts the blend prior to the final compression of the melted blend, essentially preventing agglomeration of the ingredients.

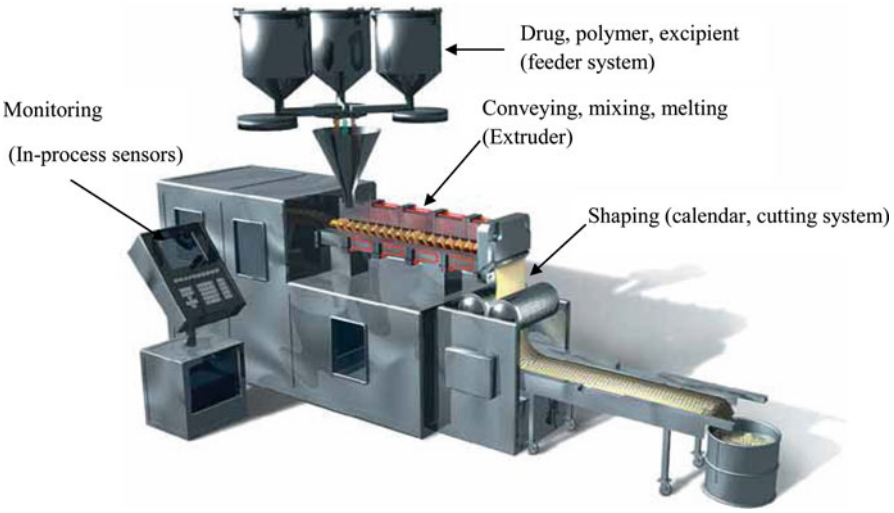


Fig. 1.6 Schematic representation of a typical pharmaceutical twin-screw extruder. (Adapted with permission from Breitenbach (2002))

A majority of the extruders manufactured for pharmaceutical applications are of twin-screw, corotating, and intermeshing types (Repka et al. 2012). As mentioned earlier, TSE overcomes the agglomeration limitation of SSE, additionally, it also offers better conveying, transport mechanisms of the feed, and provides intense mixing of the components. The rotational motion of a twin screw creates an environment of controlled temperature and pressure inside the barrel. High-capacity extruders are designed with temperature sensors and independent heating or cooling units in the barrel that efficiently maintain the individual zones at preset temperatures. The pressure arising from the friction of the moving material against the barrel walls eventually results in the ejection of material through the die cavity (Crowley et al. 2007).

The twin screws can orient in varying configurations depending on the desired level of shear and the speed of mixing or operation (Mollan 2003). Due to their efficient engineering design, adequate kneading, dispersion potential, and shorter and constant residence time (important for heat-sensitive feed material), TSEs with corotating intermeshing screws find widespread applications in pharmaceutical processing.

Although melt extrusion is considered as a unit operation, it consists of series of subprocesses as material feeding, powder conveying and degassing, melting and mixing, melt conveying and venting, and pumping, shaping, and cooling (Fig. 1.6).

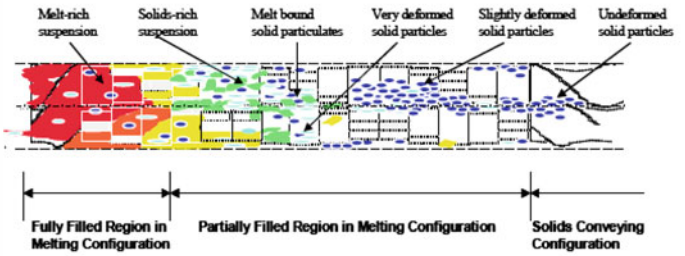
Material Feeding: Extruder feeding systems mostly control the homogeneity of the product. Gravimetric (loss in weight) or volumetric feeders are generally used for pharmaceutical extruders. A volumetric feeder that operates by the principle of volume displaced by a pumping mechanism is most suited for preblends with good

flow properties, while a gravimetric feeder employs transducers that measures loss in weight and quite consistently generates constant flow rates (Rauwendaal 2001).

Feeding of extruders can be either in the "starve-fed" or the "flood-fed" mode. For pharmaceutical processing, feeding is commonly conducted in a "starve-fed" mode, which results in efficient mixing of the feed material as opposed to flood feeding. Starve feeding uses gravimetric or volumetric feeders to dispense the material directly into screws, that prevents the accumulation of the feed material at the feed zone and thus the mass flow rate is independent of screw speed. At steady state, in a starve-fed mode, the mass flow rate at the feed zone is equal to the mass exiting the barrel and thus accumulation in the barrel is negligible. However, screw speed can have a significant influence on the residence time distribution of the feed material (Rauwendaal 2001). Feed rate, feed type (preblend or multiple), and pulsations in feeding rate influence the degree of fill, which in turn affect the homogeneity, thermal and mechanical energy input into the formulation. Additionally, the side-stuffing option can be employed for predensification of a low-bulk density powder to achieve better throughput. In case of liquid injection, a continuous stream could be achieved by maintaining sufficient backpressure to prevent clogging and variability. Moreover, feed locations on the length of barrel would influence the shear stress, temperature, and mixing experiences of the feed material. For instance, a heat-sensitive material can be added downstream to prevent thermal degradation or excessive shear stress; however, this technique may compromise its mixing capability (Schenck 2010).

Conveying and Venting: As the name indicates, conveying elements move the material from the feed section to further downstream regions in the forward flow direction. Conveying efficiency can be improved by altering certain characteristic geometric features of the conveying elements, such as flight width, pitch, and angle of helix. In addition, the internal to external diameter (Di/Do) ratio, which determines the extruder-free volume often limits the maximum feed rate, throughput, and torque attained. Sufficient venting in the feed section is essential to limit the detrimental effect on throughput due to entrained air and moisture from the feed material (Todd 1998).

Melting and Mixing: Melting of the feed material occurs by conductive thermal energy input via the heated barrel surface and by mechanical energy input supplied by the screws. The barrel heat melting process is likely to be influenced by factors such as uniform product temperature, poor thermal conductivity of the polymers, and volumetric scale-up. About 80–90 % of melting is achieved by viscous dissipation via frictional forces (including interparticle, material/wall, and material/screw friction) (Tadmor and Klein 1970; Todd 1993). The mechanical energy is mainly dissipated in three different ways: frictional energy dissipation (FED) from the frictional movement of polymer solid particles, plastic energy dissipation (PED) from the irreversible deformation of solid particulates, and viscous energy dissipation (VED) from the irreversible deformation, i.e., flow of the polymer melt. PED is essentially the energy dissipated during large and repeated plastic deformations of compacted feed stock particulates while still in the solid state and is much higher than the VED source of polymeric melts. The melting phenomenon is best described by following



				"States" of the Stream Schematic Representation Co TSE Screw Configuration
VED	PED VED (DMM)	PED	Conduction	Melting Mechanisms (Pellets)
VED	PED VED (DMM)	PED	Conduction	Melting Mechanisms (Powder)

Fig. 1.7 Schematic representation of the evolution of melting of plastic pellets or powder in a co-TSE. (Adapted with permissions from Gogos (1998))

three perspectives: degree of fill; mode of conveying; and structural states of the change as it is being transformed from loose particulates to melt-rich suspensions or fully melted streams as depicted in Fig. 1.7 (Gogos 1998).

Specific energy (ratio of mechanical energy-drive motor reading in kW to feed rate, kg/h) describes the mechanical energy input to the material by the screws per unit mass and plays an important role in scale-up and optimization of the formulation. Various screw designs and configurations directly influence the specific energy, residence time distribution, and maximum shear stress imparted among most process responses. As the material transitions from solid to melt, a distinct change in flow characteristics is observed as the result of the temperature attained, which is greater than the glass transition temperature of the one or two components of the feed material (e.g., mostly polymers). This point marks the beginning of the melt residence time of the material in the barrel. While the fluidity of the polymers accelerates the dissolution of high-melting drugs across the length, it may also affect the degradation of some heat-sensitive compounds. Thus, controlled barrel temperature and effective screw profile and screw speed may result in increased heat transfer from the system and lower localized temperature ultimately leading to desired quality attributes of the extrudates. Generally, high-pressure builds are observed at the melt/mixing sections of the extruder due to the viscous nature of the melt and minimal conveyance afforded by screw geometry that promotes back mixing and delineates other unit operations along the process length (Todd 1998).

Melting and mixing of the feed stock is a result of the combination of material characteristics (viscoelasticity), equipment parameters (screw design- pitch, number of flights, channel depth, flight width, barrel clearance, design and number of

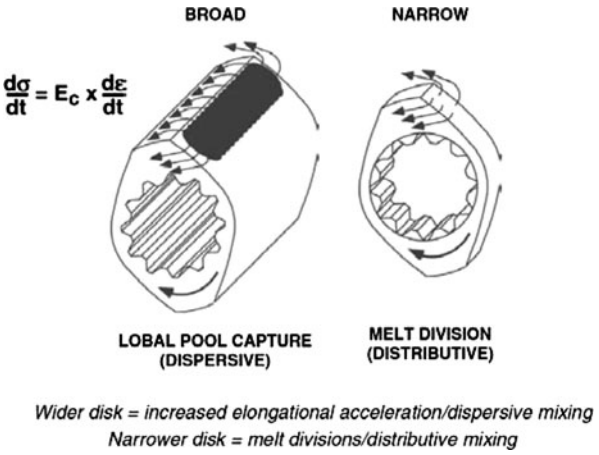


Fig. 1.8 Basic kneading section for dispersive and distributive mixing. (Adapted with permissions from Thiele (2003))

kneading paddles, length and number of mixing sections), and operational parameters, such as screw speed, feed rate, barrel temperature, and temperature imparted through viscous heat generation.

Corotating TSEs have the ability to mix the material longitudinally as well as transversely. The self-wiping nature of the two screws during rotation ensures that intermeshing TSE is self-cleaning. A screw configuration containing only conveying screw elements would mostly move material through the extruder via drag flow with minimal laminar mixing, hence, mixing or kneading elements become an essential component of screw design to attain good content uniformity. Primary mixing for melting and melt dispersion occurs in the kneading blocks or mixing elements, where alternating cycles of constant compression and expansion of the material are very conducive to supplying the forces required for rapid melting and for elongational flow of melts for both dispersive and distributive mixing. Distributive mixing is a type of mixing, wherein the material is divided and recombined in order to achieve better compositional and thermal homogeneity without distorting the individual morphological components. Distributive mixing is achieved using interrupted screw mixing elements (devices promoting division and reorientation of flow elements) and gear mixers or by using paddles with a narrow axial width (Fig. 1.8). The intense shear and shear stress facilitated by wider kneading elements mostly supports dispersive mixing with reduction in the size of morphological components and ultimately leads to molecular dispersion of the miscible components (Thiele 2003).

Melt Conveying and Venting: Residence time and residence time distribution (Di-Nunzio 2012) are important parameters and have an influence on the quality of the obtained extrudates. Residence time for a given process varies with change in screw speed or feed rate. However, screw design, temperature, and melt viscosity of the blend may also influence the residence time distribution, significantly influencing product attributes such as homogeneity and degradation. Similarly, melt residence

time, i.e., the time from which material exists in the molten state across the length of the barrel, will have implications on product attributes during scale-up.

Venting is an essential step further downstream to the mixing section, to remove residual moisture or gas formation occurred during intense melting or the mixing process. Venting or degassing can be achieved by opening the top barrel section over the conveying section often assisted by vacuum to prevent bubbling or foaming of the extrudate.

Pumping, Shaping, and Cooling: The next stage in the extrusion process is to pump the molten extrudate through a die and thereby impart a definite shape for further downstream processing. Die geometry precision control may play a role in the final product with intended applications (e.g., transdermal films), which would require a slit die, annular dies for medical tubing formation. The molten extrudate may also be processed downstream via conventional unit operations (i.e., milling and compression) and in this case precise die geometry is not critical. Mostly circular dies with multiple strands are employed for rapid quench cooling. Pellets can be produced for multiparticulate dosage forms by passing the extrudate strand through a die face-cut pelletizer (Young et al. 2002).

The extruder die is also one of the high-pressure build-up sections of the barrel with nearly 100 % screw fill. Die geometry and the viscoelastic nature of the melt determine the increase in pressure, resistance, and temperature due to viscous heat dissipation resulting in maximum product temperature. Thus, changes to die design are warranted to minimize the pressure build-up for heat-sensitive or pressure-sensitive formulations.

The molten extrudates are often cooled using a conveyor belt with compressed air, or feeding through chilled stainless steel rolls. Cooled extrudates can be further milled into powder, which is either compressed into tablets or filled into capsules. Alternatively, final shaped dosage forms can be obtained from calendaring or injection molding of the melt. These molds yield the classic tablet, capsule shapes, or custom-designed shapes to suit various applications such as denture adhesives, vaginal rings, ear inserts, or pediatric friendly (enhance the esthetic appeal of the product) designs. Some of the dosage forms (made with melt extruded material) that have been previously characterized are films (Repka and McGinity 2001; Trey et al. 2007), pellets, spherical pellets (Young et al. 2002), punched tablets (Fukuda et al. 2006), injection-molded tablets (Quinten et al. 2009), rods, and granules (Robinson and Mcginity 2000) .

1.3.2 Process-formulation Interplay

While continuous processing is a salient feature of the melt extrusion technology, it is imperative to assess the influence of engineering aspects on the product quality. Simply said, it is important to understand the complex interplay between formulation and process during melt extrusion to obtain the desired product attributes. For melt extrusion, processing conditions have a direct influence on the product quality and performance for the intended application. Several aspects of the formulation, for

instance, melt viscosity of the blend, solubility, heat and pressure sensitivity are directly influenced by processing parameters such as residence time distribution, feed rate, die design, screw configuration, and screw speed (Repka et al. 1999; Schilling et al. 2007; DiNunzio et al. 2010a). A systematic development approach regulating the key parameters that influences the critical quality attributes (CQAs) of the product would further assist in late-stage development with full optimization and scale-up using QbD principles. Hence, early development and later-stage optimization are both governed by the complex formulation and process interplay.

Lowinger (2011) extensively describes the influence of various process or engineering-related factors on the product quality. Modularity in extruder screws enabling change in screw profile may affect factors such as mechanical shear and residence time. Feed rate, type (preblend or multiple feeds), and pulsations in feeding rate, influence the degree of fill, which in turn affects the homogeneity, thermal and mechanical energy imparted into the formulation.

In addition, there are several studies describing the effect of process variables such as screw speed, barrel temperature, residence time on the product quality, and performance (Nakamichi et al. 2002; Verreck et al. 2003; Lyons et al. 2008) of melt extruded products. Liu et al. (2010) studied the dissolution behavior of indomethacin (melting point 162 °C) in Eudragit® EPO ($T_g = 48$ °C) matrices, processed using a batch mixer. The investigator identified the barrel set temperature, counterrotating twin-rotor screw speed, and residence time as important parameters that affected the dissolution behavior of the indomethacin. In addition, the study also revealed that for successful solubilization of the drug, the typical residence time for a particular process should be greater than the time needed for the drug to dissolve in the polymer melt. Both the barrel set temperature and screw speed increased the dissolution rate, which can be explained by the Noyes–Whitney equation (Eq. 1.1).

$$dC/dt = DA/h^*(C_s - C_t) \tag{1.1}$$

Their findings indicated that dissolution rates (dC/dt) of crystalline indomethacin in the molten EPO matrix could be increased by raising the temperature of the system (i.e., processing above the glass transition temperature of the carrier phase). Therefore increased equilibrium solubility (C_s) and diffusivity (D) of the drug in the molten carrier matrix was achieved due to reduced viscosity of the matrix at elevated temperatures. In addition, increased screw speed enhanced the available particulate surface area (A) of the API and decreased the boundary layer thickness (h), thereby contributing to increased diffusivity (D) and dissolution rate (dC/dt). Thus, each of the terms in the above equation (Eq. 1.1) can be altered to ultimately achieve high dissolution rates (dM/dt). Surface area (A) of the drug can be increased by micronization (Hughey et al. 2010), while increased solubility (C_s) and diffusivity (D) could be achieved by raising the processing temperature or by addition of cosolvents or plasticizers. Applying more shear (suitable screw configuration and screw speed) to the system would result in further reduction of the viscosity (decrease in boundary thickness, h) and thereby enhance the diffusivity and dissolution rate of the drug in the carrier phase. In addition, role of screw configuration in influencing the formation

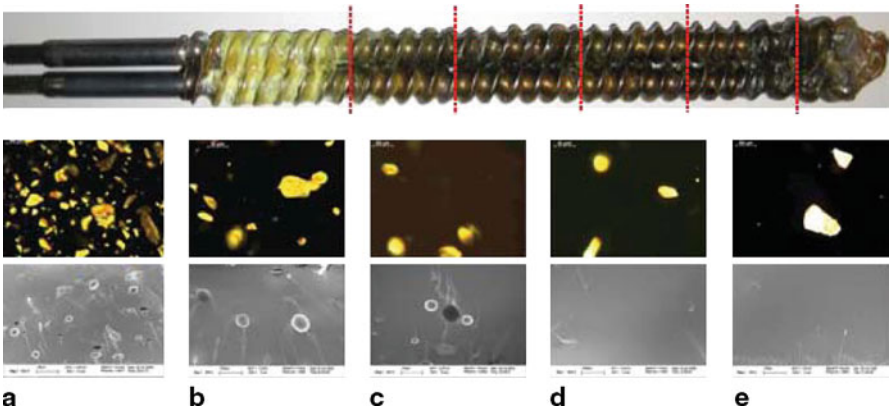


Fig. 1.9 The evolution of morphology along screw M0: polarized light micrographs (*top* row) and scanning electron micrographs (*bottom* row): **a** 8th lobe, **b** 13th lobe, **c** 19th lobe, **d** 24th lobe, and **e** 28th lobe. (Adapted with permissions from Liu et al. (2012))

of cocrystals and for melt granulations (Dhumal et al. 2010; Mu and Thompson 2012) has been reported. Additionally, Liu et al. (2012) evaluated the effect of four different screw configurations on the extent of dissolution of indomethacin in Eudragit®EPO. These researchers monitored the shifts of the indomethacin's benzoyl C=O stretch peak (1,692 cm^{-1} γ-crystal form and 1,684 cm^{-1} amorphous form) for the different screw configurations. Their findings suggested that the first kneading or mixing zones in the screw configurations promoted the transformation of crystalline indomethacin to the amorphous form. Figure 1.9 indicates that the crystalline indomethacin did not completely transform to the amorphous state until the 19th lobe when the screw without the kneading or mixing zone was used.

However, for the other three screws, which have at least one kneading or mixing zone, the transformation was complete at the 13th lobe (Fig. 1.10). FTIR analysis indicated that the first kneading or mixing zone promoted the complete dissolution of indomethacin into the EPO melt. However, their study does not identify the significance of the second kneading or mixing zone, which warrants further investigation.

Subtle changes in the processing conditions can remarkably alter the physicochemical properties of the formulations. A recent invention by a Roche scientist (Chatterji 2012) describes a novel bottom-up microcrystallization manufacturing process utilizing HME. In this case the drug substance exhibits low solubility and is also subject to extensive degradation and metabolism and hence not amenable to formulation by ASD. The patent illustrates the formation of controlled crystalline solid dispersion of API from its super cooled liquid state. The invention describes a process, wherein the crystalline API is converted to noncrystalline form by application of heat and shear up to one-fourth to three-fourth of the barrel length followed by a recrystallization zone in the remaining barrel length, wherein cooling is applied. The cooling of the barrel initiated API nucleation that promoted crystal growth while the shearing action of the screws evenly distributes the nuclei and hence controls the

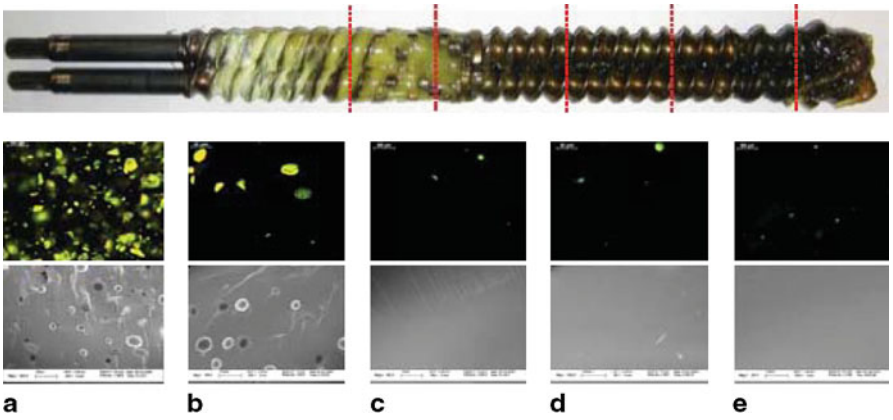


Fig. 1.10 The evolution of morphology along screw M1S: polarized light micrographs (*top* row) and scanning electron micrographs (*bottom* row): **a** 8th lobe, **b** 13th lobe, **c** 19th lobe, **d** 24th lobe, and **e** 28th lobe. (Adapted with permissions from Liu et al. (2012))

mean particle diameter of the newly formed crystalline API. The particle size of newly formed crystalline API is significantly less than the bulk API. Recrystallization of the API is controlled by carrier formulation design and HME process parameters such as barrel temperature and feed rate. The crystalline drug, dalcetrapib, is unstable in its amorphous state; hence, the aforementioned processing technique was found to be a rather suitable method of production. In addition, rapid dissolution was observed as compared to its micronized form. However, this approach faces technical challenges such as maintaining consistent batch-to-batch crystallization (particle size of crystals), and detection of residual amorphous drug content.

1.3.3 Late-stage Development: Scale-up Considerations and QbD-based Approach

In addition to providing a set of potential screening hits, early-stage development in HME also provides an insight into potential problems that may be encountered during scale-up and subsequent commercial-scale processing. Late-stage development of HME formulations particularly focuses on scale-up and adoption or optimization of process with necessary modifications to suit commercial-scale processing. Certain important material characteristics like melt viscosity, thermal sensitivity, and recrystallization potential as evaluated during early-stage development determine the ultimate scale-up strategy adopted during late-stage development.

While several authors have described scale-up approaches for HME-based formulations (Todd 1995; Dreiblatt 2003; Steiner 2003; McKelvey 2008; Schenck 2010; Lowinger 2011; Markarian 2012; Dreiblatt 2012), the present section provides a