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HOT-MELT EXTRUSION IN PHARMACEUTICAL MANUFACTURING: PROCESS PARAMETERS AND PRODUCT PERFORMANCE

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Abstract

Hot-melt extrusion (HME) has moved from plastics processing into routine pharmaceutical manufacture over roughly three decades. This review, which reports no new data, draws on published reviews and experimental papers to describe how barrel temperature, screw configuration, screw speed and feed rate shape the extrudate, and how carrier choice and drug–polymer miscibility decide whether an amorphous solid dispersion stays amorphous and dissolves faster. It also covers sustained-release matrices, in-line monitoring and the quality-by-design approach applied to the process. The literature shows consistent dissolution gains for poorly soluble drugs, but comparisons across studies are hampered by differing equipment, scale and stability protocols. Scale-up rules and long-term physical stability remain the main gaps.

1. INTRODUCTION

A large share of the compounds that reach development today dissolve too slowly to be absorbed well. The biopharmaceutics classification system places them in classes II and IV, and the proportion of such molecules in discovery pipelines has grown as screening has favoured lipophilic, high-affinity leads [1, 2, 3]. Formulators have several ways round the problem, from particle size reduction and salt formation to lipid systems and complexation, but amorphous solid dispersions remain one of the few routes that can raise apparent solubility several-fold without altering the molecule [3, 4]. The idea

is not new. Chiou and Riegelman catalogued the approach in 1971 [4]. What changed was the manufacturing method. Solvent evaporation and pan fusion are awkward to scale, whereas extrusion, borrowed from the plastics and food industries, is continuous and solvent-free [5, 6].

In hot-melt extrusion (HME) a blend of drug, polymer and often a plasticiser or surfactant is conveyed by rotating screws through a heated barrel, softened or melted, mixed under shear and pushed through a die. Breitenbach described the route from process to delivery technology in 2002 [6], and the two-part review by Crowley and colleagues followed in 2007 [5, 7]. Later reviews widened the scope to sustained release, taste masking, films and implants [8, 9, 10]. Marketed tablets made this way are now described in the regulatory-facing literature [11, 12]. This review asks a fairly narrow question: which process parameters matter, how they interact with the formulation, and what the published work says about the performance of what comes out of the die.

2. EXTRUDER DESIGN AND PROCESS PARAMETERS

Single-screw extruders convey and pump well but mix poorly, so they are used mainly for simple melts and shaping. Co-rotating, intermeshing twin-screw machines dominate pharmaceutical work because the self-wiping screws give a narrow residence-time distribution and strong distributive mixing [13, 14]. The screw is built from modular elements: conveying sections that move material forward, kneading blocks that knead and shear it, and sometimes reverse elements that hold the melt back to raise the degree of fill. Nakamichi and co-workers showed that the kneading paddles, together with screw speed and water content, determined how completely a drug was dispersed in the carrier [15]. In practice the screw profile is the single most influential design choice, and it is often fixed early and then left alone.

Barrel temperature is the parameter most people think of first. Raising it lowers melt viscosity, eases conveying and speeds the dissolution of drug into the molten polymer, but it also raises the risk of degradation of a heat-labile drug or carrier [11, 13]. Liu and colleagues extruded indomethacin with Eudragit E PO and reported that barrel temperature, screw speed and screw configuration each altered dissolution behaviour, and that the effect of any one of them depended on the settings of the others [16]. That interaction is the main lesson. One-factor-at-a-time studies, still common in the older literature, can mislead because the optimum for temperature shifts when the screw profile changes.

Residence time distribution is the quantity linking screw design to product quality. It is measured by adding a tracer to the feed and following its appearance at the die, and in intermeshing twin-screw machines the typical residence time is of the order of a minute or two, with a spread that depends on the screw profile and fill [13, 14]. A wide distribution means that some of the material experiences far more heat than the average, which matters for heat-sensitive compounds. Narrow distributions are easier to achieve with starve feeding and with conveying elements in place of long reverse sections, and they make the melt history of each part of the extrudate more uniform [13, 15].

Screw speed and feed rate act mostly through residence time and fill. A faster screw shortens the time the material spends in the barrel and raises shear, which can help dispersive mixing but also heats the melt through friction; a higher feed rate at constant speed fills the screw channels more fully and lengthens residence time [13]. Many groups prefer starve feeding, in which the feeder rather than the screw sets throughput, because it makes the process easier to control and to scale. Fluctuating feed gives fluctuating melt pressure at the die, and extrudates then vary in diameter and density. Practical experience, and most of the review literature, suggests that a steady, well-calibrated gravimetric feeder repays its cost quickly [11, 14].

Every formulation has a processing window bounded below by the temperature needed to soften the carrier and above by the temperature at which drug or polymer starts to degrade. Plasticisers widen the window by lowering the glass transition temperature of the carrier. Not every drug needs to melt: in

many dispersions the crystalline drug dissolves into the softened polymer well below its own melting point, a mechanism that lets heat-sensitive compounds be processed at moderate temperatures [17, 18]. Sarode and colleagues proposed predictive tools linking drug–polymer interaction, processing temperature and supersaturation behaviour, an effort that moves the choice of settings away from pure trial and error [18].

Scale-up deserves a place in this discussion because most published work is done on 11 to 18 mm laboratory extruders, while manufacture needs far larger machines. Common approaches keep the specific mechanical energy, the residence time or the degree of fill constant, or hold the geometry similar while the screw diameter grows. Thiry and colleagues pointed out that heat transfer scales differently from throughput: the surface available for cooling grows more slowly than the volume of melt, so a recipe that stays cool in a small barrel may overheat in a large one [13]. Process models and dimensionless numbers help but still need verification with real material, and regulatory reviews of marketed products stress that the scale-up route should be justified with data rather than assumed [12, 14].

3. CARRIER SELECTION AND MISCIBILITY

Carriers for extrusion include polyvinylpyrrolidone and its vinyl acetate copolymer, cellulose ethers, polymethacrylates, polyethylene glycols and amphiphilic graft copolymers. The choice rests first on thermal behaviour, since the polymer has to soften at a temperature the drug can survive, and then on the glass transition of the finished dispersion. Hancock and Zografi argued that amorphous material is best stored well below its glass transition, a margin of about 50 °C being a common rule of thumb, because molecular mobility rises steeply as the two temperatures approach [19]. The Gordon–Taylor equation gives a first estimate of the glass transition of a drug–polymer mixture from the values of its components [20]. It assumes ideal mixing, so measured values often differ, and the difference is itself informative [21].

Whether the drug and polymer are miscible at the intended loading decides whether the dispersion is a true solid solution or a supersaturated system waiting to crystallise. Solubility parameters calculated by group contribution were an early screening tool. Greenhalgh and co-workers found that a difference below about 7 $MPa^{1/2}$ generally predicted miscibility, while a difference above about 10 $MPa^{1/2}$ predicted immiscibility [22], and Forster and colleagues applied the same idea with thermal analysis to choose excipients for two poorly soluble drugs [23]. Thermodynamic models based on Flory–Huggins theory go further, estimating drug solubility in the polymer as a function of temperature [24]. Djuris and co-workers fitted such a model to carbamazepine–Soluplus extrudates and used it to predict miscibility [25].

Plasticisers and surfactants are added to lower processing temperature and torque, and sometimes to improve wetting. The trade-off is easy to overlook. Anything that lowers the glass transition of the extrudate also lowers the margin that protects it in storage. Ghebremeskel and co-workers used solubility parameters to select polymer–surfactant combinations and tested how processable they were, showing that a surfactant could act as a plasticiser but that the combination had to be chosen carefully [26]. Reviews of poorly soluble drug extrusion repeat the same advice: use the least plasticiser that achieves a stable, reproducible melt [8, 10].

Drug loading is the quantity that ties these choices together. A dispersion loaded below the equilibrium solubility of the drug in the polymer should be thermodynamically stable, whereas one loaded above it is supersaturated and depends on kinetics, namely the high viscosity and low mobility of the glassy polymer, to stay amorphous [21, 24]. Marsac and colleagues showed how solubility estimates could be used to set a ceiling on loading [24]. Higher loading is attractive because it keeps tablet size down, yet the published dispersions that remained stable through storage are mostly those with moderate loadings, and the temptation to push the limit has to be balanced against the cost of failure months after release [3, 17].

Particle and pore properties of the milled extrudate also affect dissolution, though they are discussed less often than chemistry. A finely milled extrudate presents more surface and wets faster, but very fine powders of tacky polymers flow badly and may agglomerate on contact with water, forming a gel layer that slows release. Some carriers dissolve by erosion from the surface, others swell and release drug through a gel, and the choice between these behaviours is made at the formulation stage, long before the first extrusion trial [10, 11].

4. PRODUCT PERFORMANCE

The findings most often reported for processing variables, carriers, miscibility prediction and monitoring tools are collected in table 1. Dissolution is the performance measure that appears in almost every study. For poorly soluble drugs, extrusion into a hydrophilic or amphiphilic carrier commonly produces faster and more extensive dissolution than the crystalline drug, often with a period of supersaturation [17, 18]. Lakshman and colleagues showed that melt extrusion could produce a high-energy amorphous dispersion that was both physically and chemically stable, which matters because the same shear and heat that create the amorphous state can also drive degradation [17]. The size of the gain depends on drug loading, carrier, and the particle size of the milled extrudate [3, 10].

Table 1: Findings reported for process variables, carriers, miscibility prediction and monitoring in hot-melt extrusion

Item	Reported finding	Ref.
Barrel temperature	Higher temperature lowers melt viscosity and aids dissolution of drug in polymer, but raises the risk of degradation of heat-labile components.	[13, 16]
Screw speed and feed rate	Set residence time, shear and degree of fill; dissolution effects in indomethacin–Eudragit E PO depended on the other settings.	[13, 16]
Screw configuration	Kneading paddles improved dispersion of drug in the carrier and gave more uniform extrudates.	[14, 15]
Feed method	Steady, starve-fed throughput gave stable melt pressure and better control of extrudate dimensions.	[11, 13]
Soluplus graft copolymer	Carbamazepine dispersions were extruded successfully, and a thermodynamic model predicted drug–polymer miscibility.	[25]
Ethylcellulose	Extruded and directly compressed matrix tablets differed in structure and drug release.	[27]
Extruded matrices	Milled extrudate could be compressed into sustained-release tablets with a controlled release profile.	[28, 29]
Solubility parameters	A difference below about 7 $MPa^{1/2}$ was associated with miscibility and above 10 $MPa^{1/2}$ with immiscibility.	[22, 23]
Flory–Huggins fitting	Estimated drug solubility in polymer against temperature, helping to judge the loading that stays stable.	[24, 25]
In-line Raman	Allowed drug–polymer quantification and solid-state characterisation during extrusion.	[30, 31]
Thermal analysis	Detects glass transition and residual crystallinity, but heating during the measurement may change the sample.	[19, 32]

Sustained-release products are the second major use. Here the carrier is usually water-insoluble or slowly eroding, such as ethylcellulose, and the extrudate is milled and compressed or cut into pellets. Crowley and colleagues compared ethylcellulose matrix tablets made by direct compression and by extrusion, and reported that the manufacturing route changed the matrix structure and the way the drug was released [27]. Zhang and McGinity had earlier described how extruded matrices could be turned into sustained-release tablets [28]. Islam and co-workers used a quality-by-design strategy to develop extruded sustained-release formulations, tying

release behaviour to defined process settings [29].

Dissolution method choice shapes how those results should be read. Compendial tests in a single buffer can hide the difference between a dispersion that holds supersaturation and one that precipitates within minutes, which is why non-sink conditions and transfer from acid to neutral media are increasingly used. Polymers such as the cellulose ethers and vinylpyrrolidone copolymers are described as precipitation inhibitors, prolonging the supersaturated state long enough for absorption [17, 18]. The link from such a profile to exposure in people depends on the drug's permeability, as the biopharmaceutics classification makes plain [1].

Comparison with other ways of making an amorphous dispersion is worth a brief note. Spray drying handles heat-labile drugs better and gives fine particles, but needs a common solvent and a drying step, while extrusion avoids solvent and runs continuously yet exposes the drug to heat and shear [9, 10]. Reviews generally treat the methods as complementary and recommend choosing by drug stability and by the physical form needed downstream, not by habit [11, 12].

The entries in the table fall into four groups (fig. 1). Process variables account for the largest number, which reflects where research effort has gone: parameters such as temperature, speed and screw profile are easy to vary and easy to report. Carriers come next. Miscibility prediction and monitoring tools are represented by fewer entries, and that imbalance is telling. Fewer papers test whether an in-line measurement can replace an end-product test, and fewer still follow dispersions through to bioavailability studies [30, 32]. The count is only a rough guide to the published record, since a single study often covers several rows.

Beyond oral solid dispersions and matrices, extrusion has been used for taste masking, transmucosal and transdermal films, and implants. In taste masking the drug is embedded in a polymer that resists dissolution in the mouth, and extrusion avoids the organic solvents that casting would need. Films made by extrusion tend to be thicker and less uniform than cast films but can carry drug in a solvent-free matrix [8, 9]. Implants and intravaginal rings extend the idea to long-acting delivery, where the polymer must remain mechanically sound for weeks, and where residual crystalline drug can alter release over time [11, 33]. These uses share a feature with the oral products: performance depends on the same handful of process and formulation variables, applied with different targets in mind.

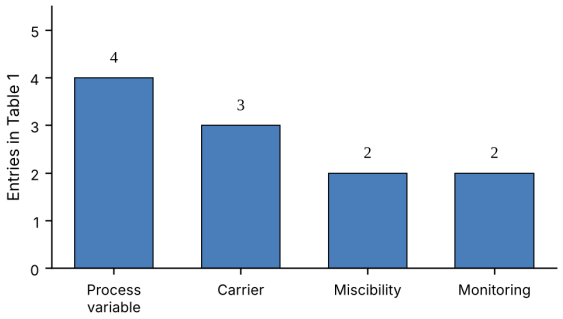


Fig. 1: Number of entries in table 1 by topic group

Stability and storage need the same attention as dissolution. Extruded dispersions of a model drug in an acrylate carrier have been characterised by thermal, microthermal and spectroscopic methods, which shows how physical state can be judged and followed on storage under controlled temperature and humidity [34], and for amorphous extrudates the humidity arm is the demanding one. Baird and Taylor reviewed thermal analysis techniques for evaluating the properties of amorphous dispersions and cautioned that heating during measurement can itself change the sample, so that a single calorimetric trace may under- or over-state residual crystallinity [32]. Complementary techniques such as powder X-ray diffraction and spectroscopy are usually needed before a dispersion can be called amorphous with confidence [19, 32].

5. ANALYTICAL TOOLS AND QUALITY BY DESIGN

Offline characterisation of extrudates relies on differential scanning calorimetry for glass transition and residual melting, powder X-ray diffraction for crystallinity, and infrared or Raman spectroscopy for drug–polymer interaction, supplemented by dissolution and content uniformity tests. The regulatory push towards process analytical technology, set out by the US Food and Drug Administration in

2004, encouraged measurement inside the process rather than after it [31]. Saerens and co-workers demonstrated in-line Raman spectroscopy for drug–polymer quantification and solid-state characterisation during extrusion, showing that composition and form could be tracked as the material left the barrel [30]. Near-infrared probes and ultrasonic sensors have been described as well, though with fewer published validations [11, 33].

Quality by design gives the process-level view. ICH Q8(R2) asks developers to define the quality target product profile, identify critical quality attributes, and link them to critical material attributes and process parameters through experimentation, ideally producing a design space [35]. For extrusion, screw speed, feed rate, barrel temperature profile and screw configuration are the usual candidate parameters, while dissolution, assay, degradants and solid-state form are the usual attributes [13, 29]. Simões and colleagues, writing on the route towards filing a new drug application, noted that continuous manufacturing and real-time monitoring fit naturally with an extrusion line and that regulators had by then reviewed several filings based on it [12].

Specific mechanical energy deserves explanation because it appears in so many papers. It is the mechanical work put into each kilogram of material, calculated from motor torque and screw speed, and it summarises how hard the screws have worked the melt. Two runs with the same barrel temperature can differ greatly in specific energy, and with it in the degree of drug dispersion and the extent of thermal and shear degradation [13, 16]. Because torque is recorded continuously by the extruder, it also provides a free, real-time indicator of process drift, and a rising torque at constant settings often warns of feed problems or moisture changes before any laboratory result is available [14, 30].

Raw material variability feeds into all of this. Polymers differ in molecular weight and moisture content between batches, drug particle size changes how quickly crystals dissolve in the melt, and hygroscopic carriers take up water that acts as a temporary plasticiser. Nakamichi and colleagues included water content among the variables that altered the preparation of dispersions in a twin-screw extruder [15]. Specifying and testing incoming materials is therefore part of controlling the process, and the quality-by-design literature treats material attributes as inputs equal in importance to machine settings [29, 35].

6. LIMITATIONS AND FUTURE DIRECTIONS

Several limits apply to this review as to the literature it summarises. Most studies use one or two model drugs and a short list of polymers, so general rules are drawn from a narrow base. Equipment varies from small laboratory extruders to pilot lines, and stated settings are not always comparable. Thiry and colleagues reviewed critical process parameters and scale-up and concluded that no universal scaling rule exists, because heat transfer, mixing and residence time scale differently with screw diameter [13]. Heat-labile and high-melting drugs remain difficult, and the literature on them is dominated by case-by-case solutions [11, 33]. Because this is a narrative review, selection of papers was not systematic.

7. CONCLUSION

Hot-melt extrusion works because it combines heat, shear and mixing in a single continuous step, and the published record shows it can turn poorly soluble crystalline drugs into dispersions that dissolve faster and, in sustained-release forms, release more steadily. The result depends on a set of linked choices rather than any single setting. Screw profile, temperature, speed and feed rate act together, and they act on a formulation whose carrier, plasticiser and drug loading fix the glass transition and the miscibility [13, 16, 22, 24].

For practice, the evidence supports choosing carriers with miscibility prediction in hand, working within a defined processing window, monitoring the process in-line where possible, and testing physical stability under humid conditions before claiming a stable product [30, 32, 34, 35]. The main gaps are scale-up rules, long-term stability data and in vivo confirmation. Until those are filled, extrusion remains a technique that rewards careful

development rather than one that can be applied by recipe [12, 13].

8. ABBREVIATIONS

API-Active pharmaceutical ingredient, BCS-Biopharmaceutics classification system, DSC-Differential scanning calorimetry, HME-Hot-melt extrusion, ICH-International Council for Harmonisation, PAT-Process analytical technology, QbD-Quality by design, Tg-Glass transition temperature

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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