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Teaser A glance at hot-melt extrusion within the pharmaceutical industry and its challenges, where a systematic step-by-step approach for product development is proposed, QbD discussed and regulatory matters highlighted through case studies.

Hot-melt extrusion in the pharmaceutical industry: toward filing a new drug application

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Abstract

The pharmaceutical development of amorphous solid dispersions (ASDs) by hot-melt extrusion (HME) is briefly reviewed. A systematic step-by-step approach is presented, where thermodynamics, polymer screening, multivariate statistics and process optimization are combined, to increase the success of HME-based drug product development. The quality by design (QbD) concept is introduced and applied to HME. Steps and tools for its effective implementation are provided, including risk assessment highlighting crucial points. The technical and scientific specificities of HME-based ASDs are discussed in light of the current paradigm of drug development and in-line with regulatory guidelines from the ICH regions. Case studies of recently approved HME products are presented.

Introduction

Hot-melt extrusion (HME) has been revealed as a successful technology for a large spectrum of applications in the pharmaceutical industry, with proven robustness for numerous drug delivery systems (DDS) [1,2]. Some of the most well-known applications are for taste-masking of drugs [3–5], solubility enhancement of poorly water-soluble compounds [6–10], controlled [11–13], extended [14], sustained [15,16] and targeted [17–21] drug delivery, and also preparation of nanoparticles [22–24]. The versatility of HME for the development and manufacturing of very different (Fig.1) DDS has made it a technology that shifted the entire paradigm of pharmaceutical industry research and manufacturing. The enhancement of solubility and bioavailability (BA) through the manufacturing of amorphous solid dispersions (ASDs) is the primary use of HME [25–31], as indicated by the multiple papers and patents. This process not only offers the inherent free energy benefits of an amorphous system but also provides a maximum specific surface area and higher saturation solubility, which ultimately increase drug solubility and BA [27].

Solid dispersions are systems where one component is dispersed in a carrier, and where the whole system appears to be solid [32–37]. A drug can remain molecularly dispersed within the polymer or exist in a crystalline or amorphous phase, and the solubility characteristics of these

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Marta obtained her PharmD at the Faculty of Pharmacy of University of Coimbra in 2013 and has been working in the pharmaceutical industry since then. In 2014 she started to work as a formulation scientist in the R&D department of Bluepharma Indústria Farmacêutica SA, where she developed her interests for formulation and manufacturing process development and optimization, upscale, statistical design of experiments, data analysis, quality by design and mechanistic modeling. She is a PhD student within the program: Drugs R&D in Pharmaceutical Technology, which is carried out in Bluepharma in collaboration with the University of Coimbra. Her research interests center on bioavailability enhancement of poorly soluble drugs through amorphous solid dispersions and methods of manufacturing thereof.

Rui Pinto Rui Pinto has a degree in pharmaceutical sciences and a PhD in pharmaceutical chemistry. An author of >30 publications in the field of natural product chemistry and new green chemical process, his scientific interests also focus on the interaction of chemical process with pharmaceutical development. In 2015, he joined Bluepharma Indústria Farmacêutica SA, where he currently has the role of managing R&D projects. Actually, his main research areas are implementation of strategies to support clinical development programs of investigational medicinal products and the development of new technological platforms for drug delivery, with special emphasis in the design of approaches to overcome drug-substance-related poor performance of finished dosage forms.

Sérgio Simões has a degree in pharmaceutical sciences, a Master's degree in chemical engineering and a PhD in pharmaceutical science. He has built a rapport as a scientist, an entrepreneur, an investor and as a decision-making executive in the pharmaceutical industry. Since 2001 he has been a member of the board of Bluepharma Indústria Farmacêutica SA and from 2012 a manager of Blueclinical, Lda. His role has been instrumental in the launch of several technology-based companies, including Luzitin and Treat U, as well as in the running of investment ventures such as A2B, SA or Biocant Ventures. He currently holds a position as an associate professor with habilitation at the Faculty of Pharmacy of the University of Coimbra, Portugal. Apart from his academic work, his interests include research fields related to pharmaceutical biotechnology, with particular emphasis on the development of targeted nanocarriers for drug and nucleic acid delivery aiming at their application for gene therapy. Over the past years, he has gained a significant expertise on the development, industrial transfer and manufacturing of medicines for the European and US markets.

https://doi.org/10.1016/j.drudis.2019.05.013

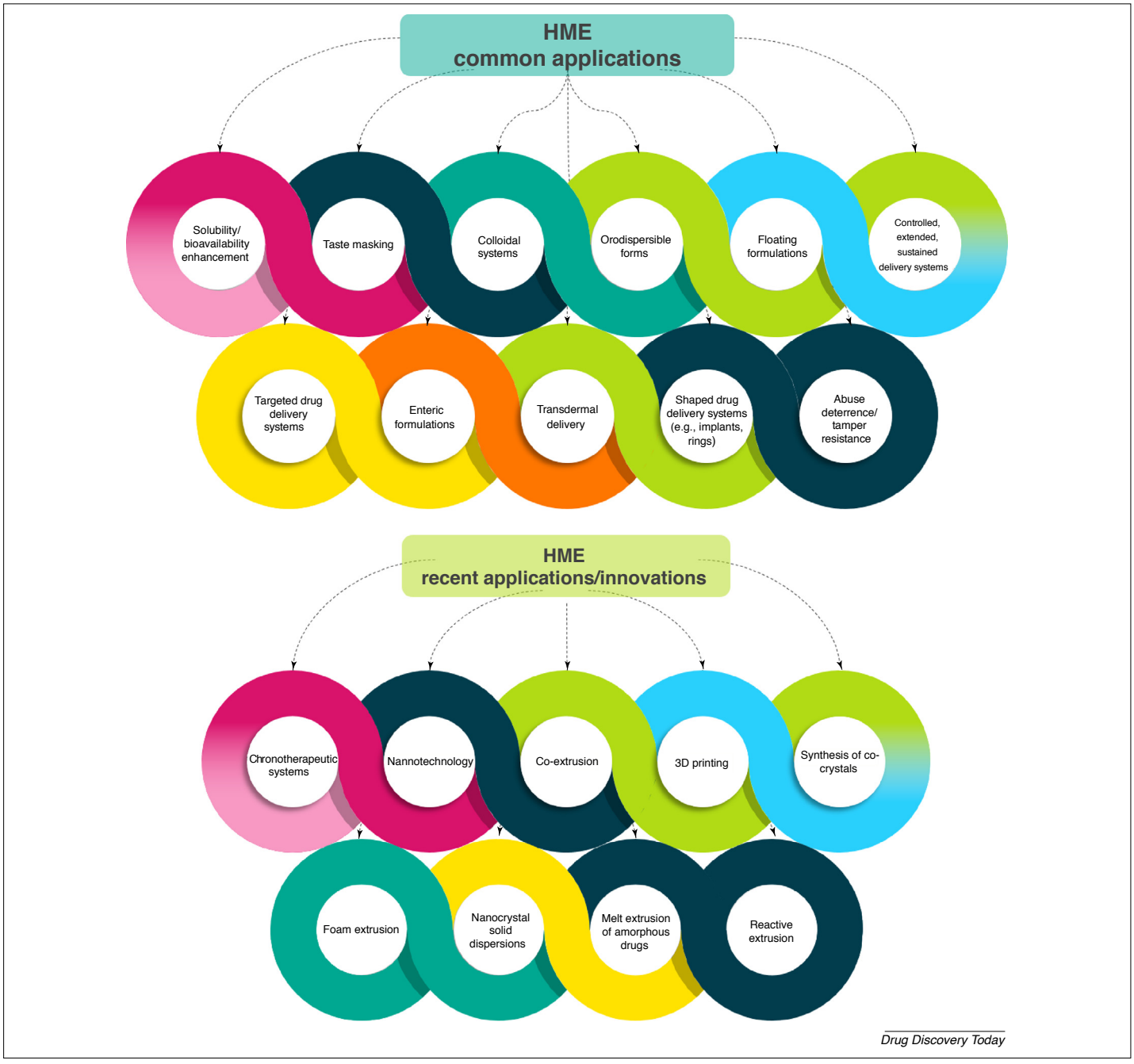

FIGURE 1

Common and recent applications of HME technology [28–31].

types of solid dispersions differ [27,38]. When amorphous, the drug tends to revert to the most stable crystalline form [27] and this is, in fact, the main issue associated with ASD [32–37]. This phenomenon leads to the failure of the entire formulation strategy of using ASDs to improve BA and justify, at least partially, why there are only a few ASD-based formulations in the market [36,39]. This work intends to drive the formulation scientist into HME technology with a focus on the pharmaceutical industry, with the aim of developing and submitting new products to regulatory authorities. A systematic step-by-step approach for the development of HME products is presented. As a core in product development, the quality by design (QbD) paradigm applied to HME is discussed, including steps and tools for its implementation and a risk assessment that can be followed to support dossier filing. The focus is primarily on frequently ignored topics, as useful and practical approaches, rather than heavy and unfeasible ones in the routine of product development, from early development to regulatory approval. Moreover, possible questions from dossier reviewers are listed and reflect technical and scientific specificities of this type of formulation. Finally, the latest approvals are analyzed as case studies within the QbD paradigm.

TABLE 1

Currently marketed HME products [27,30,39,58–65]

Pharmaceutical form	Commercial name	Owner	Drug(s)	Therapeutic indication	Polymer	HME purpose
Ophthalmic insert	Lacrisert®	Merck	–	Dry eye syndrome	HPC	Shaped (rod) system
	Ozurdex®	Allergan	Dexamethasone implantable device	Macular edema	PLGA	Shaped system
Implants	Zoladex®	AstraZeneca	Goserelin	LHRH agonist	PLGA	Shaped (rod) system
	Depot-Profact®	Sanofi Aventis	Buserelin	Carcinoma of the prostate gland	PLGA	Shaped (rod) system
	Probuphine® (2016, USA)	Titan[a]	Buprenorphine	Opioid dependence	EVA	Shaped (rod) system
Devices	Implanon®	Schering-Plough	Etonogestrel	Contraceptive	EVA	Shaped (rod) system
	NuvaRing®	NV Organon	Etonogestrel / ethinylestradiol	Contraceptive	EVA	Shaped (ring) system
	Annovera® (2018, USA)	Therapeutics MD	Ethinylestradiol/ segesterone acetate	Contraceptive	Silicone	Shaped (ring) and multilayer system
Oral	Kaletra®	Abbott	Lopinavir/ritonavir	HIV	Copovidone	Amorphous Dispersion
	Isoptin® SRE	Abbott	Verapamil	Hypertension	HPC/HPMC	Shaped system (oval)
	Covera-HS®	Pfizer	Verapamil HCl	Hypertension and angina pectoris	HPC	Melt granulation
	Nurofen Meltlets lemon®	Reckitt Benckiser Healthcare	Ibuprofen	Analgesic	HPMC	Melt Granulation
	Norvir®	Abbott	Ritonavir	HIV	PEG-glyceride	Amorphous Dispersion
	Gris-PEG®	Penidol Ph.	Griseofulvin	Onychomycosis	PEG	Crystalline dispersion
	Rezulin®	Parke-Davis	Troglitazone	Diabetes	PVP	Amorphous dispersion
	Cesamet®	Meda Pharmaceuticals	Nabilone	Antiemetic drug	PVP	Solid dispersion
	Adalat SL®	Bayer	Nifedipine	Antianginal agent	HPMC/PEO	Controlled release
	Eucreas®	Novartis	Vildagliptin/ metformin HCl	Diabetes type 2	HPC	Melt granulation
	Zythromax®	Pfizer	Azithromycin enteric-coated multiparticulates	Antibiotic	Pregelatinized starch	Melt granulation
	Fenoglide®	Life Cycle Pharma	Fenofibrate	Dyslipidemia	PEG 6000	Solid dispersion
	Noxafil®	Merck	Posaconazole	Antifungal	HPMCAS	Amorphous dispersion
	Onmel®	Merz	Itraconazole	Onychomycosis	HPMC	Amorphous Dispersion
	Palladone®	Purdue Pharma	Hydromorphone HCl	Pain relief	HPMC/ethylcellulose[b]	Controlled release
	Nucynta®	Janssen	Tapentadol	Pain relief	PEO/HPMC/PEG	Controlled release and abuse-deterrent
	Opana ER®	Endo Pharmaceuticals	Oxymorphone HCl	Pain relief	PEO/HPMC/PEG[b]	Controlled release
	Belsomra® (2014, USA)	Merck	Suvorexant	Insomnia	Copovidone	Amorphous Dispersion
	Viekirax® (2014, EU)/ Technivie® (2015, USA)	AbbVie	Ombitasvir, paritaprevir and ritonavir	Hepatitis C virus	Copovidone/ vitamin E polyethylene glycol succinate	Amorphous Dispersion (3 separate ASDs)
	Viekira pak® (2014, USA)	AbbVie	Ombitasvir, paritaprevir, ritonavir and dasabuvir	Hepatitis C virus	Copovidone	Amorphous Dispersion (3 separate ASDs of ombitasvir, paritaprevir and ritonavir)
	Venclyxto® (2016, EU) Venclexta® (2016, USA)	AbbVie	Venetoclax	Chronic lymphocytic leukemia	Copovidone/ polysorbate 80/colloidal silicon dioxide	Amorphous Dispersion
	Maviret® (2017, EU) Mavyret® (2017, USA)	AbbVie	Glecaprevir/pibrentasvir	Hepatitis C virus	Copovidone/ vitamin E polyethylene glycol succinate	Amorphous Dispersion

Abbreviations: HPChydroxypropyl cellulose; PLGApoly(lactic-co-glycolic acid); EVAethylene-vinyl acetate; PVPpolyvinylpyrrolidone; HPMChydroxypropyl methylcellulose; PEGpolyethylene glycol; PEOpolyethylene oxide; HPMCAShydroxypropyl methylcellulose acetate succinate; HMEhot-melt extrusion.

[a] Two additional discreet arm implants are under development by Titan Pharmaceuticals (preclinical phase): ropinirole for the treatment of Parkinson's disease and T_3 hormone for hypothyroidism through the ProNeura™ drug delivery platform.

[b] Polymers present in the formulation of the drug product are probably used for the preparation of the extrudate.

Overview of HME-based marketed drug products

Current interest in HME is growing rapidly with >500 papers published in the scientific literature during the past decade [40]. HME is employed to produce different DDS, such as for oral administration: granules [41–43], pellets [44,45], films [46,47] and tablets [48,49]; but also transdermal [50,51], transmucosal [52,53] and subcutaneous (implants) [54–57] administration. Although there is a huge potential for formulating poorly soluble drugs into ASDs, few have been commercialized so far (Table 1) [27,30,39,58–65]. Nevertheless, this trend is clearly changing as more and more HME-based drug products appear in the pipeline of many pharmaceutical companies.

Lately, there have been new product submissions to the FDA and to the European Medicines Agency (EMA). In 2016, a new implant for the treatment of opioid dependence, containing buprenorphine, was approved by the FDA. Probuphine® is a 6-month treatment for opioid dependence, the first to be approved and the only one so far. It consists of four subcutaneous implants of 26 mm each, placed in the underside of the upper arm, providing a continuous and steady release of low-dose buprenorphine [66]. In October 2018, the FDA also approved Annovera® (segesterone acetate and ethinyl estradiol vaginal system) – a combined hormonal contraceptive that marked the first time a vaginal ring could be reused for 1 year [67].

In what concerns oral dosage forms, novel products have also been approved. Belsomra® (suvorexant), an orexin receptor antagonist and the first of its class, was approved in 2014 by the FDA [68]. It is an ASD prepared by HME to maximize BA. The team selected to extrude the compound with a pH-independent solubility polymer, copovidone [69], and observed that the tablet hardness was related to disintegration, dissolution and absorption [28]. Viekirax® (EU) [Technivie® (USA)], approved in 2014 by the EMA and in 2015 by the FDA, is also a very interesting product from a technical point of view because all three drugs (ombitasvir, paritaprevir and ritonavir) are individually converted into amorphous materials by HME to enhance their BA. Only then the individual extrudates are combined, tableted and coated [65]. Venetoclax, approved as Venclyxto® in the EU and as Venclexta® in the USA for the treatment of chronic lymphocytic leukemia, is also manufactured by HME as a solid dispersion owing to the very poor water solubility [70]. Mixtures of drug and copovidone with surfactants (Aerosil® and Tween®) were extruded to enhance its absorption, and the formulation was then patented [71], demonstrating improved BA when manufactured by HME. More recently, Maviret® (EU) [Mavyret® (USA)] was approved by the EMA and FDA for the treatment of chronic hepatitis C. The drugs glecaprevir and pibrentasvir are poorly water-soluble and they are also individually formulated as ASDs to increase the apparent aqueous solubility and obtain adequate *in vivo* absorption [72].

To our knowledge, there are already two ophthalmic inserts, four implants and two vaginal rings approved so far, and many more are under development. However, the focus is still on oral administration, where HME is mostly applied to manufacture ASDs, and the aim is to overcome the poor solubility and to promote absorption *in vivo*. Lessons learned from the past approvals are that simple formulations can be used and manufactured by HME to solve several formulation and delivery issues. This is sometimes the only chance that challenging drugs have to be taken to patients, with the desired delivery, the adequate dose and a suitable safety profile.

Pharmaceutical development of HME-based formulations

Pharmaceutical development aims to provide robust knowledge through the application of systematic approaches that allow designing a quality product and its manufacturing process consistently. The information and knowledge collected from development and production should provide the scientific understanding to support a design space, drug product specifications and process controls. The complete understanding of the formulation and process is consolidated in the Common Technical Document (CTD; section 3.2.P.2) and then used to submit a

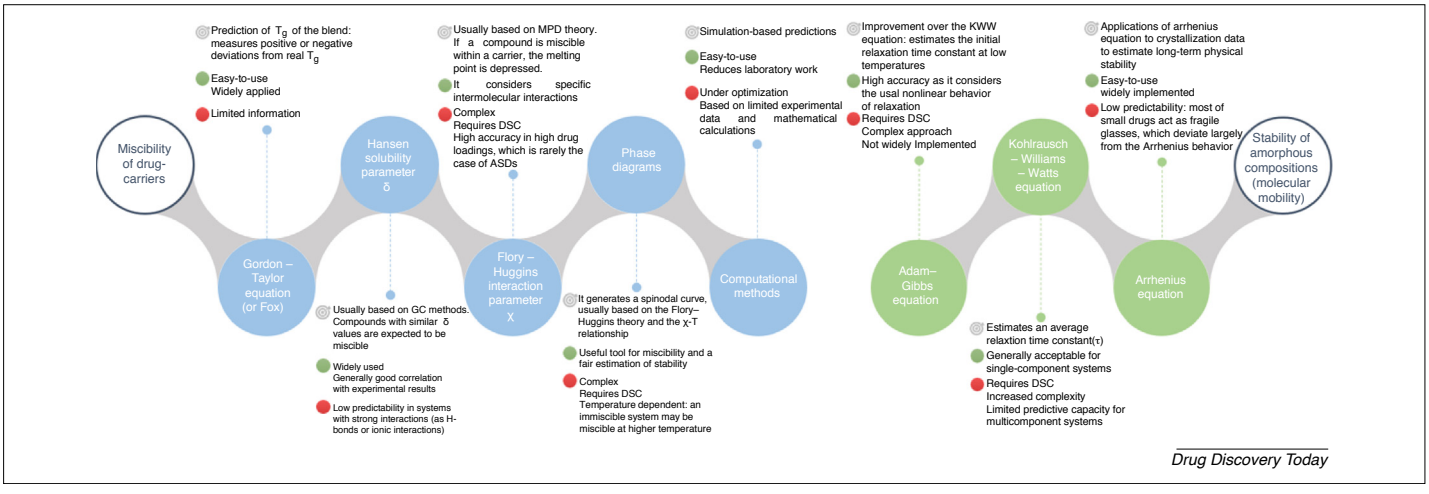

FIGURE 2

Thermodynamic assessment of amorphous compositions: applications, advantages and limitations. Abbreviations: Tg – Glass transition temperature; GC – Group Contribution; MPD – Melting Point Depression; DSC – Differential Scanning Calorimetry; ASDs – Amorphous Solid Dispersions; KWW - Kohlrausch – Williams – Watts.

new drug application to the competent authorities [73]. In HME-based drug products, a robust pre-formulation assessment is the key to a successful development. A step-by-step approach, starting with the thermodynamic evaluation of several systems, followed by a polymer screening test coupled with multivariate statistical analysis, is useful to rapidly identify the most promising HME systems. This is the way to avoid wasting time, money and effort in failed compositions.

Thermodynamic predictions and considerations

The selection of a suitable carrier mainly depends on the solubility and miscibility of a drug–polymer system, polymer physicochemical properties, stability and prerequisites of final dosage forms. Therefore, physical and chemical properties of drug substances and possible carriers should be carefully evaluated before starting the development of HME-based formulations. The miscibility of drugs and carriers is usually one of the first issues to be evaluated. This is essential to guarantee adequate drug load and chemical interactions between the components, which is valuable to optimize process parameters and product performance on dissolution [74]. However, there is no established procedure to select excipients for HME to date [75]. Several methods have been described to predict miscibility with the carrier, usually applying thermodynamic predictions in an attempt to guide formulation development rationally. Predicting miscibility is a difficult task, and the results are crucial [28] for the course of the development work. Some of the more common approaches include the prediction of T_g of the blend using the Gordon–Taylor equation [76] (or the simplified form by Fox [77]), the calculation of the Hansen solubility parameters [78], the Flory–Huggins theory and the calculation of the interaction parameter (χ) [79], and also the construction of phase diagrams [31] (Fig. 2). A review of thermodynamic and computational methods has been recently published by DeBoyace and Wildfong [80].

The Gordon–Taylor (or Fox) equation [81,82] is a commonly used approach to predict the miscibility of drug–polymer blends in the pharmaceutical industry setting, as reflected in publications from Novartis [83], Merck [84], AbbVie [85], Johnson & Johnson (J&J) [86] and Lundbeck [87]. One of the most recent examples is from J&J, where the Gordon–Taylor equation was applied in the assessment of the impact of the molecular structure of sorafenib and its fluorinated form, regorafenib, in interactions and consequent miscibility with polymers. A positive deviation of T_g from the prediction of the sorafenib formulation as opposed to the regorafenib one was an indication of stronger interactions, confirmed by NMR and computational methods [86]. Another example was published by Lehmkemper *et al.*, where the Gordon–Taylor equation was used to model the T_g of ASDs of acetaminophen and naproxen – both manufactured by HME. The calculations were in line with experimental results for naproxen, but a negative deviation was observed for acetaminophen, which indicated weak interactions with the polymer. The results were validated by stability studies until 18 months [85].

In what concerns the Hansen solubility parameters (δ) [82,88,89], group contribution methods are often used to estimate δ, to avoid time-consuming tests and potentially inaccurate results. These methods are easy to use [80], and there are already some well-known approaches, like those by Hoy [90] or Hoftyzer and van Krevelen [78]. The calculation of solubility parameters and their application to ASDs, in the academia and in the pharmaceutical industry, is still one of the most applied approaches owing to its relative simplicity. There are even attempts to improve group contribution parameters and to develop new values based on solids, as the method published by Just *et al.* [91] verified with ASDs manufactured by HME and film casting. Several publications describe the use of solubility parameters in an industry setting, namely by AstraZeneca [92], Merck [93], Sandoz [94], GlaxoSmithKline [95], ACG Pharma [96], Aizant [25,97], Hoffmann-La-Roche [98], Boehringer-Ingelheim [99], among many others [100–103]. Wlodarski *et al.* reported the use of δ for the prediction of miscibility between itraconazole and two polymers: polyvinyl alcohol and copovidone [93]. A work in collaboration with Aizant recommended using δ as part of a systematic approach to design solid dispersions and applied it to the development of a cilostazol ASD [25]. Pawar and co-workers developed an ASD of efavirenz by HME, where two polymers were selected based on the prediction of miscibility through the Hansen parameters [96]. Although δ can be useful for the fast screening of potential carriers, inadequacies in theory often lead to the exclusion of good candidates and require additional experimental work to confirm the interpretations. This was verified and published by AstraZeneca, where 54 drug–polymer combinations were experimentally assessed for miscibility, and results were compared with δ results. The predicted δ did not match the experimental data, and some reasons were pointed out as relating to the negligence of intermolecular interactions [92].

These weaknesses have led to the development of more-complex methods, such as the calculation of the Flory–Huggins interaction parameter (χ), usually through the application of the melting point depression (MPD) theory [79]. This method is also used by the pharmaceutical industry and is probably the most popular approach, with research work published by J&J [104], Amgen [105], Bayer [106], Genentech [107], AbbVie [85,108], Bristol-Myers Squibb [109–111], AstraZeneca [92], Lundbeck [87,112,113], Boehringer-Ingelheim [114], Dow and Dispersion Technologies [115,116], Hoffmann-La Roche [117,118], Abbott [119], Merck [120], Pfizer [79], Aizant [97], among others [121,122]. In 2018, lapatinib was formulated by rotary evaporation and by HME, and the polymers were selected based on several thermodynamic assessments, including the Flory–Huggins equation [105]; and Rask *et al.* reported the solubility of four drugs in three different polymers determined and extrapolated to room temperature through the Flory–Huggins model. The authors also presented an interesting decision tree for the selection of the most suitable thermal method to determine the Flory–Huggins model based on the physicochemical characteristics of the drug and the carrier [104]. Similar findings were found by Chen *et al.*, where the solubility of a poorly water-soluble drug in different polymers was assessed through the Flory–Huggins interaction parameter, and the results matched the experimental data well [106]. Earlier, the assessment of acetaminophen and naproxen solubility in polymeric excipients such as povidone and copovidone, calculated with three models including Flory–Huggins, was published by Lehmkemper and co-workers. The results were in line with the experimental solubility data; however, the Flory–Huggins method underestimated the effect of acetaminophen miscibility on stabil-

ity [85]. The characterization of molecular interactions by ^{13}C NMR and Fourier-transform infrared spectroscopy (FTIR) enabled the understanding of ketoconazole–polymer system release, which was commanded by the polymer dissolution rate, intermolecular interactions and mixture homogeneity. The interaction parameter between the drug and four polymers was applied to predict miscibility, and the results matched the experimental data [110]. The MPD method was also used to predict drug miscibility of a model drug in different polymers. Soluplus® was the selected polymer, supported by the optimized stabilization capacity [108]. Although largely used by the pharmaceutical industry, χ failed to predict miscibility in a recent study from AstraZeneca, where 54 drug–polymer combinations where assessed for miscibility [92]. In fact, most of the publications to date, from academia and the pharmaceutical industry, describe the use of thermodynamic models like the Flory–Huggins method, although they were never intended to be applied to systems with strong interactions such as H-bonds [123]. Recent models that permit intermolecular interactions are undoubtedly needed to guide ASD development.

Another common tool within the industry is the construction of phase diagrams, which are usually based on the Flory–Huggins theory [31]. Phase diagrams depict the relationship between the free energy of blending and composition, usually considering drug load [124]. A group in collaboration with DisperSol Technologies constructed phase diagrams of albendazole–polymer binary mixtures from the Flory–Huggins theory to assess miscibility of ASDs, manufactured by HME or spray-drying [125]. In other work, the use of phase diagrams to predict miscibility of acetaminophen and naproxen ASDs has been reported; however, the compositions were modeled not by the Flory–Huggins theory but through the perturbed-chain statistical associating fluid theory and by the Kwei equation [126]. Gumaste and co-workers published a prediction of miscibility based on ternary phase diagrams of itraconazole–polymer-surfactant, identifying the blend hypromellose acetate succinate plus poloxamer 188 as an optimal surface-active carrier system for ASDs [127]. The use of phase diagrams has also been described by many other pharmaceutical companies, such as AstraZeneca [128,129], Hoffmann-La Roche [118] and J&J [130]. Still, phase diagrams are temperature dependent, and an immiscible system could, therefore, become miscible if the temperature increases [124]. New miscibility prediction methods are being developed, such as the MemFis system by Evonik [131], but the predictions of miscibility are generally based on limited experimental data and mathematical calculations, presenting inherent limitations.

The stability of the amorphous compositions is known to be influenced by miscibility of the drug within the carriers [75]. To predict physical stability, which is closely linked with molecular mobility, a number of thermodynamic equations exist, such as the Arrhenius [132], the Kohlrausch-Williams-Watts (KWW) [133] and the widely used Adam–Gibbs (AG) equation [133,134] (Fig. 2). Despite recognized utility in the ASD area and physical stability, these equations are not widely implemented by the pharmaceutical industry in routine product development. The Arrhenius and the KWW models cannot always predict the shelf-life of a product accurately [124]. Although considered complex for routine application, Graeser *et al*. applied the AG equation to calculate values of relaxation time (τ) of 14 different drugs analyzed through differential scanning calorimetry (DSC). Through DSC and a Matlab software script developed by the authors, a five-step method to calculate τ through the AG equation was described [135]. However, the same group also found that below T_g, which is the common storage temperature for pharmaceuticals, τ could not correlate with the experimental physical stability, indicating poor prediction-ability of this parameter [136]. Despite their complexity and even some inaccuracy, these approaches are slowly being taken by development teams. However, there is still the need for a more complete approach, combining, for instance, experimental results, thermodynamics theory and computational simulations [75], to finally be able to overcome the barriers of ASD development.

Screening approaches and multivariate statistical analysis of results

A systematization of a rational approach to design solid dispersions is crucial for a successful, fast and low-cost development, which avoids promising formulations being prematurely eliminated from experimental studies. Ideally, strategies should be efficient enough for assessing many binary and ternary – or with a higher order – combinations (drug/polymer/surfactant) to identify systems with synergistic interactions promptly, for subsequent in-depth experimental study. The most common approaches for screening excipients for HME formulations are based on solvent-evaporation methods, DSC analysis, hot stage microscopy (HSM) and melt-based methods. Solvent-evaporation methods are probably the most common in the industry setting, because of their simplicity [127] and low cost [137]. Some studies have been published, describing ways of automating and miniaturizing the screening of excipients in a high-throughput manner, for instance by Teva [127], Catalent [138], Aizant [25], Hoffmann-La Roche [137], Merck [139], among others [140]. In particular, Gumaste and co-workers reported the film-casting technique to determine the miscibility of ternary systems (polymer-drug-surfactant) [127]. However, DSC studies, HSM or melt-based methods have the advantage of applying heat, which can be beneficial when the manufacturing process under study is HME. For instance, Kyeremateng *et al*. combined DSC and a mathematical algorithm to construct complete solubility curves of drug–polymer systems, which was verified with ASDs of two model drugs: naproxen and ibuprofen [141], whereas work conducted by Boehringer-Ingelheim scientists described the use of HSM to evaluate mixtures of drug–polymer with or without surfactants or pH modifiers. The HSM analysis showed that the drug was utterly miscible in copovidone at ratios of 1:2 or 1:3 at ~195 °C and in povidone at 1:3 at ~200 °C; but in cellulose-based polymers the drug was only partially miscible even at higher temperatures. This method enabled the identification of one- or two-phase systems and led to a fast scale-up to clinical batches [99]. More recently, Auch and co-workers noticed discrepancies between a solvent-based screening method and experimental results for ASDs, and therefore took the challenge of developing a new method using heat and a melt-based approach [142]. Enose and his group published a different approach designated as hot melt mixing [143], and a miniaturized extrusion device (MinEx) used for formulation screening has been developed by Hoffmann-La Roche [144].

There are a few reports from the pharmaceutical industry, such as those by Hoffmann-La Roche [137], Aizant [25], AbbVie [141],

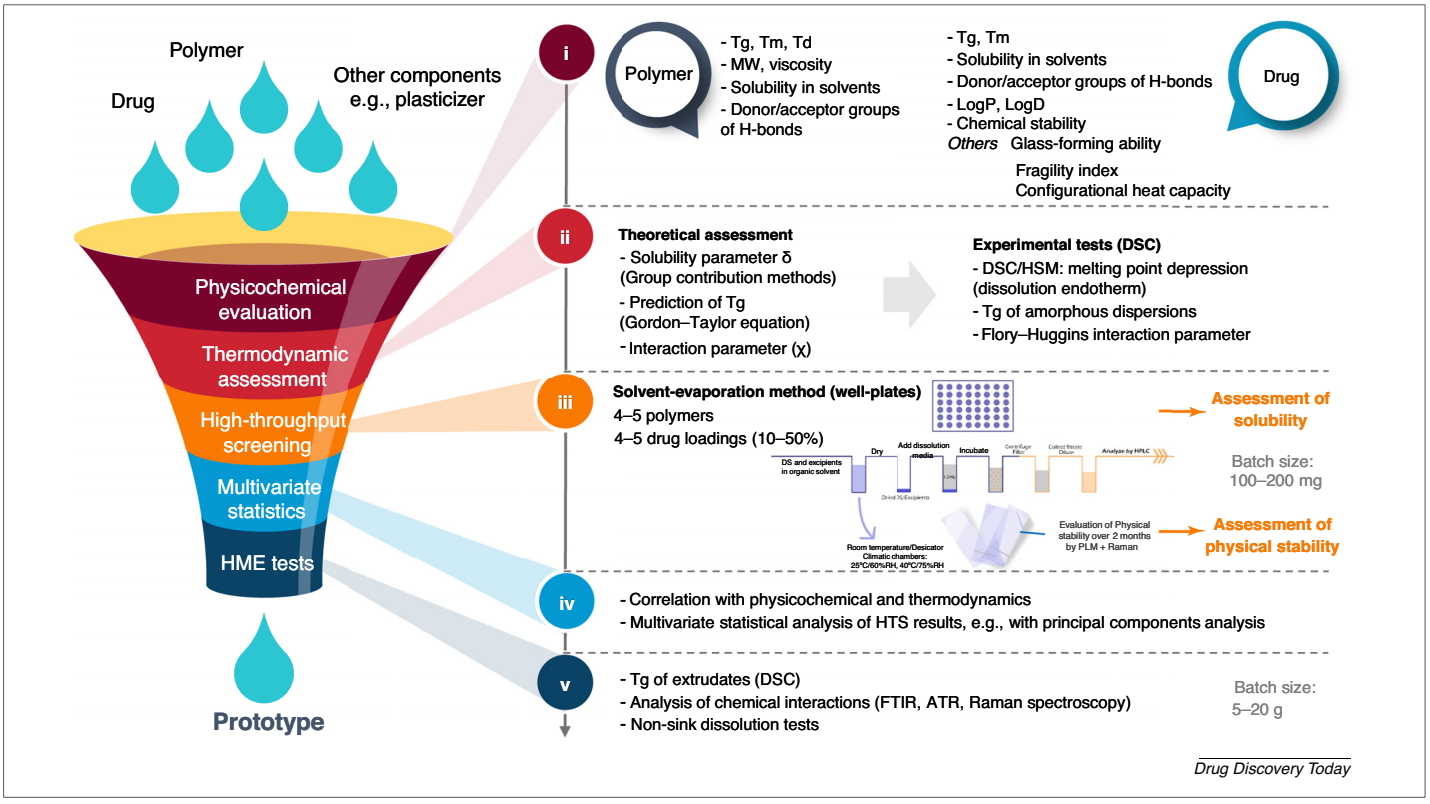

FIGURE 3

A structured approach to the development of amorphous solid dispersions (ASDs), divided into five stages. (i) Physicochemical evaluation: in-depth evaluation of physicochemical properties of the drug and potential carriers. (ii) Thermodynamic assessment: preliminary thermodynamic assessment of potential compositions, which might be supported by experimental calorimetry tests. (iii) High-throughput screening: experimental screening of carriers by a miniaturized solvent-evaporation technique for solubility assessment. Thin films are evaluated by PLM under stability for physical stability. (iv) Multivariate statistics: data analysis and identification of the most promising systems and drug loads through multivariate statistical analysis such as the principal components analysis. (v) HME tests: small-scale HME tests, focused on the dissolution (in non-sink conditions) and the potential for interactions. Abbreviations: Tm, melting temperature; Tg, glass transition temperature; Td, degradation temperature; MW, molecular weight; DSC, differential scanning calorimetry; HSM, hot-stage microscopy; PLM, polarized light microscopy; HME, hot-melt extrusion; FTIR, Fourier-transform infrared spectroscopy; ATR, attenuated total reflectance.

Boehringer-Ingelheim [99,145] and Piramal [143], that present a proposal for a systematic approach for the identification of promising compositions for HME. In general, thermodynamic evaluation is recommended and associated to screening techniques. A comprehensive overview of various miniaturized assays can be found in the literature by Shah *et al.* [146]. Based on the literature and our own experience in the development of HME-based products, a proposal for a structured screening approach is presented in Fig. 3. This methodology reflects the usual techniques, based on physicochemical principles and thermodynamic assessment of the drug and the polymer, with the aim of maximizing success rates and reducing risks. One of the main advantages is including the assessment of physical stability at the early stages during product development.

This approach is divided into five stages. During the first stage, an in-depth evaluation of physicochemical properties of the drug and potential polymers is performed. Then, in the second stage, excipients are assessed through solubility parameters, prediction of T_g and interaction between the components. This preliminary evaluation can be complemented with experimental tests such as calorimetry, where the T_g can be confirmed (and the potential for interactions inferred through comparison with the theoretical value), the depression of the melting point evaluated and, eventually, the interaction parameter determined. As an outcome, excipients with a high probability of miscibility and chemical interaction are taken to the next (third) stage, where an experimental screening of carriers is proposed in a high-throughput and miniaturization manner (HTS). The solvent evaporation method is probably the most widely used approach, and is therefore proposed, but applied not only to the assessment of miscibility and solubility enhancement but also to a preliminary experimental evaluation of physical stability. In the latter, thin films on glass slides are subjected to a short stability study and evaluated by polarized light microscopy (PLM) for birefringence. This evaluation can be complemented with other nondestructive techniques for detection of crystallinity, such as X-ray diffraction or Raman spectroscopy. In the fourth stage, all analytical results obtained from the initial assessment and the screening phase experiments are collected and assessed. Owing to the massive load of results, namely from the HTS, one usually needs to apply statistical analysis multivariate approaches such as the principal components analysis method. This is used to identify with confidence (statistical confidence) the most promising systems and drug loads that will be subjected to small-scale HME tests (fifth stage). The fifth stage is the confirmation, where the focus is the dissolution (in non-sink conditions) and the potential for interactions,

assessed by DSC and spectroscopy. At the end of this process, one or two promising prototypes are usually identified. However, new methods are still being developed, such as the recently published thermal analysis by structural characterization (TASC) [147], and more new approaches are expected in the next couple of years.

HME tests: from first extrusions to process optimization (prototype)

Several pieces of work published by the pharmaceutical industry describe extrusion tests, namely the selection of promising formulations, preliminary extrusion tests, process development and, in some papers, even process optimization. Most of them come from the past 2 years, which is a clear indication of the relevance of HME in the pharmaceutical industry. Companies such as Amgen [105,148], Bayer [45], Amneal [149], Merck [150,151], Hoffmann-La Roche [144], AbbVie [152,153], Novartis and Genentech [154], Dow [155], Boehringer-Ingelheim [99], ThermoFisher Scientific in collaboration with BASF [156], Evonik [157], ThermoFisher Scientific [158] and Novartis [35,159,160] have active research in the HME field. In their work with lapatinib, Hu and co-workers showed that material attributes (such as drug loading and solid state) and process parameters (such as extrusion temperature) affect manufacturability and solubility significantly [105]. A dual-polymeric system was developed by Hormann *et al*. using nimodipine as a model drug and it was found that the shear stress was the most relevant factor for the performance of the ASD [45]. An interesting application of HME has been described by Gajera *et al*. to dry an aqueous nanosuspension. Process parameters such as feed rate, temperature and screw speed were studied, and the statistical analysis revealed that the first two factors are significant and affect the performance of the end product [149]. Comparison of drug substance incorporation in an ASD by HME and spray-drying was reported by Zhang and co-workers [150]. Novartis scientists reported a HME injection molding prototype of griseofulvin, where critical process parameters (CPPs) of the downstream processing step were carefully studied [154]. A highly sensitive platform based on torasemide was shown to enhance HME process understanding, namely the dynamic environment inside the extruder and the thermal and hydrolytic effects caused by the process [152]. The thermally sensitive drug gliclazide was studied by HME, through the optimization of screw design, machine setup, temperature and screw speed [155]. Indeed, in addition to formulation, the process is crucial for the quality attributes of HME products. This is why HME process development is performed carefully, step-by-step and usually in three main stages: the preliminary extrusion tests, the process development and the process optimization. This reflects the usual procedure applied by the industry, with the aim of avoiding wasting time, money and effort in failed candidates. A summary is depicted in Fig. 4.

For the first extrusion tests, which are no more than a preliminary assessment of extrusion feasibility, the aim is to define general processing conditions to be used. These conditions are based on drug substance and the physicochemical properties of the excipient, and also some considerations about the extrusion

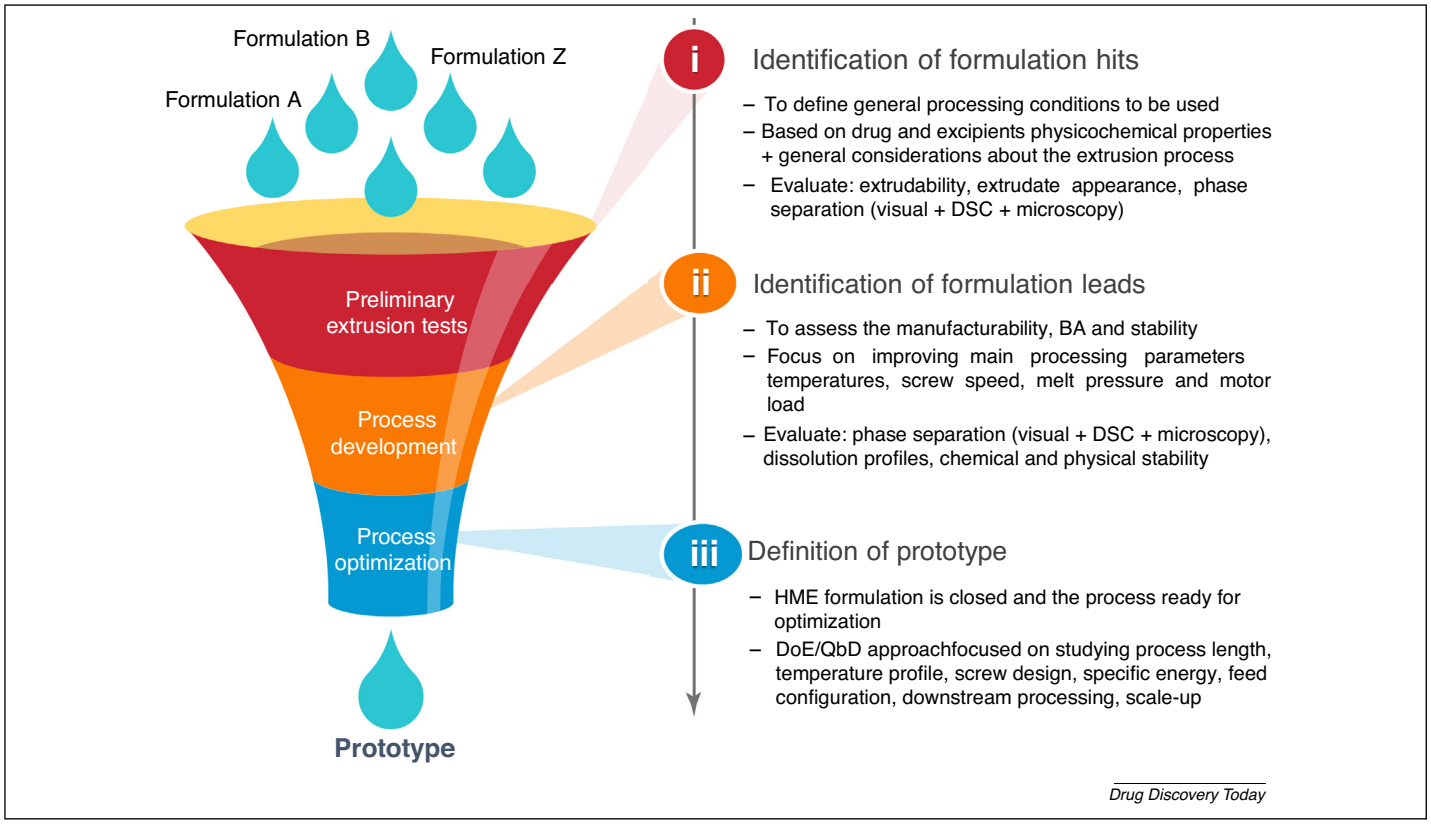

FIGURE 4

Flowchart for the development of hot-melt extrusion (HME)-based formulations divided into three main stages. (i) Preliminary extrusion tests: to define general processing parameters. (ii) Process development: to assess extrudability, *in vitro*/*in vivo* release and physical stability. (iii) Process optimization: based on QbD concepts. Abbreviations: DSC, differential scanning calorimetry; BA, bioavailability; DoE, design of experiments; QbD, quality by design.

process, for instance solid phases are to be considered [58]. Recommended process temperatures of different polymers and approaches for the thermal processing of challenging formulations have been recently reviewed by LaFountaine *et al.* [161] and should be considered by formulation scientists.

The next stage is dedicated to developing the process further. The selection of optimal processing parameters depends on the chemical stability of all the ingredients, as well as physical and chemical properties of the blend, namely the T_m of the drug, T_g of the carrier, processing temperature, drug miscibility within the polymer and melt viscosity [27]. It includes a set of experiments used to assess the manufacturability, BA and stability of ASDs prepared by HME. Following extrusion, the product is milled for further evaluation: drug dissolution profiles, chemical and physical stability, where ideal compositions will have no recrystallization upon storage. Testing in animal models is recommended to support the choice of the prototype [58,162]. Results from each topic (manufacturability, BA and stability) contribute to the overall ranking of the systems. In general, BA is considered a priority because it is usually the most important issue [58].

When the lead formulation and rough process are identified, the HME formulation is closed and the process ready for optimization. The main HME process parameters recommended for evaluation are process length, temperature profile, screw design, specific energy, feeding configuration, downstream processing and the impact of upscale [58,163]. Process development requires careful analysis of the influence of not only each variable but also interactions between variables, because they influence crucial attributes of the product [58]. A statistical experimental design approach (design of experiments, DoE) should support the development work, managing experimental data and decoupling multivariate interactions [164]. A comprehensive review of physicochemical parameters to be studied when designing and optimizing a HME process was published in 2018 by Censi and Gigliobianco [74], where different analytical techniques are described and its utility located within HME products development.

Product and process understanding through QbD

The concept of QbD was established to promote a better understanding of pharmaceutical products and manufacturing processes not only at any phase of the development cycle but also during commercial production and it is promoted by regulatory authorities, namely the FDA and EMA [165,166]. According to the International Conference on Harmonization (ICH) Q8 (R2), 'quality cannot be tested into a product but must be incorporated by design' [73]. Essential elements of the pharmaceutical development are the quality target product profile (QTPP), the critical quality attributes (CQA), the critical material attributes (CMAs) and the critical process parameters (CPPs) (Fig. 5) [166–168]. Typical QTPPs for amorphous products are an acceptable BA and pharmacokinetics profile, mainly when BCS class II or IV are concerned, and adequate stability, physical and chemical, having a minimum shelf-life of 2 years. To achieve these goals, CQAs require an in-depth study throughout the development process, namely acceptable levels of degradation, acceptable crystallinity (residual), suitable solubility and dissolution rates. For drug and excipients, CMAs can include T_m, T_g of the carrier, miscibility, thermal stability, drug load, melt viscosity, particle size, product flow, among others, which are all highly variable from product-to-product. The CPPs in the extruder can be considered to be residence time, melt temperature, screw speed, feeding rate, screw design and an energy component that can be defined as shear stress or specific energy input [158,169]. These CPPs are not easily defined during extrusion because shear, temperature and

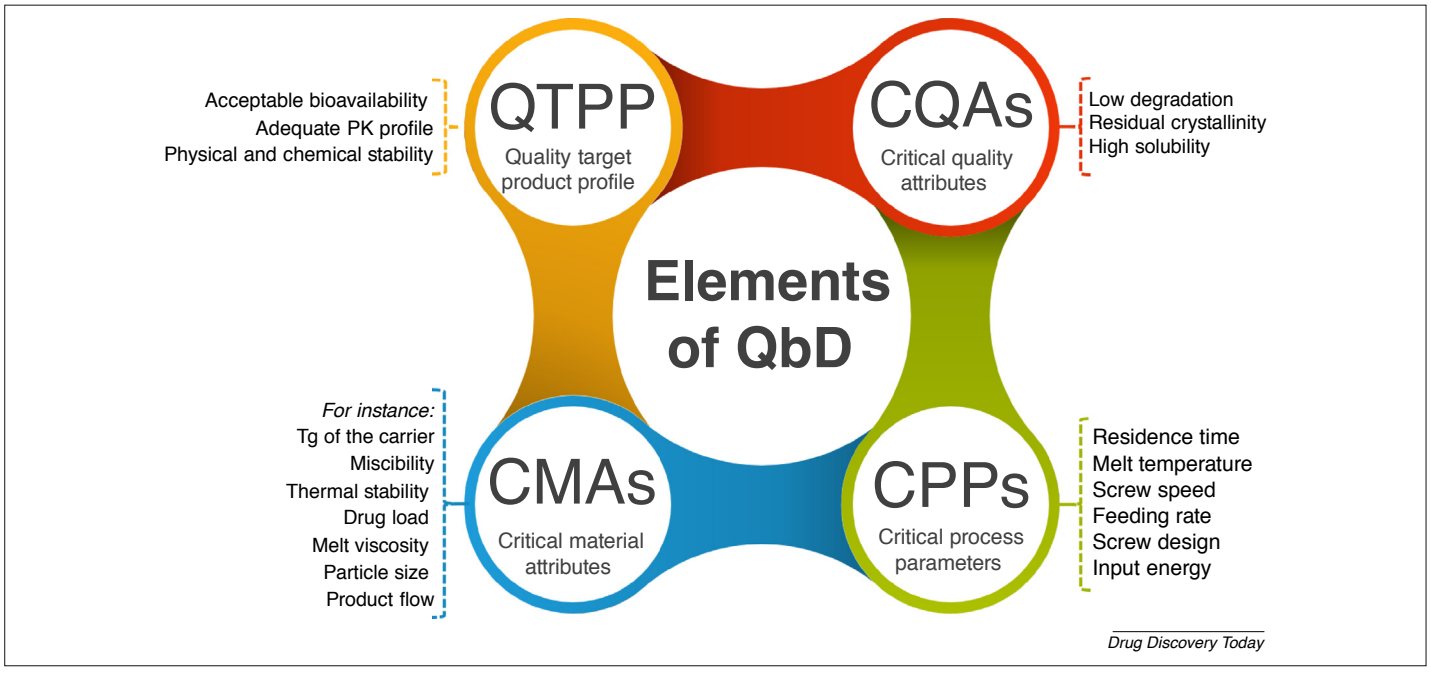

FIGURE 5

Elements of QbD with examples adapted for HME products. Abbreviations: QTPP - Quality Target Product Profile; PK – Pharmacokinetics; CQAs - Critical Quality Attributes; CMAs - Critical Material Attributes; Tg – glass transition temperature; CPPs - Critical Process Parameters.

time are distributional in nature. Therefore, they should be managed based on controllable parameters, such as screw design, screw speed, process temperatures and feed rate [169]. Moreover, it is important to keep in mind that environmental conditions can also have a role, namely the relative humidity in hygroscopic formulations and the room temperature for the cooling rate [170] when cooling is performed on a conveyor belt. The difference between QbD for a new product and generic products only exists in the first step of the process: the definition of the QTPP. For a new drug approval (NDA), the target profile is still not defined whereas, for the abbreviated new drug approval (ANDA) product, the QTPP is known and established by the reference product [171].

Steps and tools for QbD implementation in HME products

A complete QbD study involves a very well defined roadmap [165,170]. In summary, first, the QTPP must be set, based on scientific knowledge and its relevance *in vivo*. Then, the formulation and the manufacturing process are studied to ensure the predefined profile (CQAs). During this stage, one should determine what the material attributes are or the process parameters that are crucial (CMAs and CPPs) or significant sources of variability, performed through risk assessment methodologies [167]. Once they are set, a DoE should be applied to link CMAs and CPPs to CQAs and get enough information of how these factors impact QTPP [168]. This leads to the study and definition of the design space, which means determining the real values that can be applied during product manufacturing that lead consistently to the desired quality profile [166,170,172]. A complete QbD still includes a control strategy and continuous monitoring and improvement [167,168]. This is the general roadmap for QbD development, but a nine-step example applied to HME is provided in Fig. 6.

To correctly implement QbD during product development, it is crucial to know three important tools: the risk assessment, the DoE and the process analytical technologies (PATs). Considering the QbD philosophy and the ICH Q8(R2) recommendations, risk assessments at the beginning and throughout the HME product development process are crucial to success. Probably the most common tools are the construction of Ishikawa diagrams and the failure mode and effects analysis (FMEA) [167]. Risks in the Ishikawa diagram are divided into categories, whereas in the FMEA the failure modes that have the greatest chance of causing product failure are identified and translated into a ranking [167]. Several examples of Ishikawa diagrams applied to HME processes have been published [29,96,154,157,167,170,172], as well as an example of a FMEA [157]. Another common tool for risk assessment is the risk estimation matrix (REM), especially useful for identifying factors for DoE studies and design space estimation, because it only considers the severity and the probability of occurrence, excluding the detection parameter of FMEA. This is the main advantage of REM, because no parameters are excluded from the DoE owing to easy detection. It is the tool used by the FDA in their examples of pharmaceutical development report for ANDA submissions [173,174]. As far as we know, no such example for HME is available in the literature, and Table 2 depicts an initial risk assessment based on REM of a HME process applied to the manufacturing of an ASD. The REM was created through a semiquantitative analysis, where each process parameter was ranked as high, medium or low

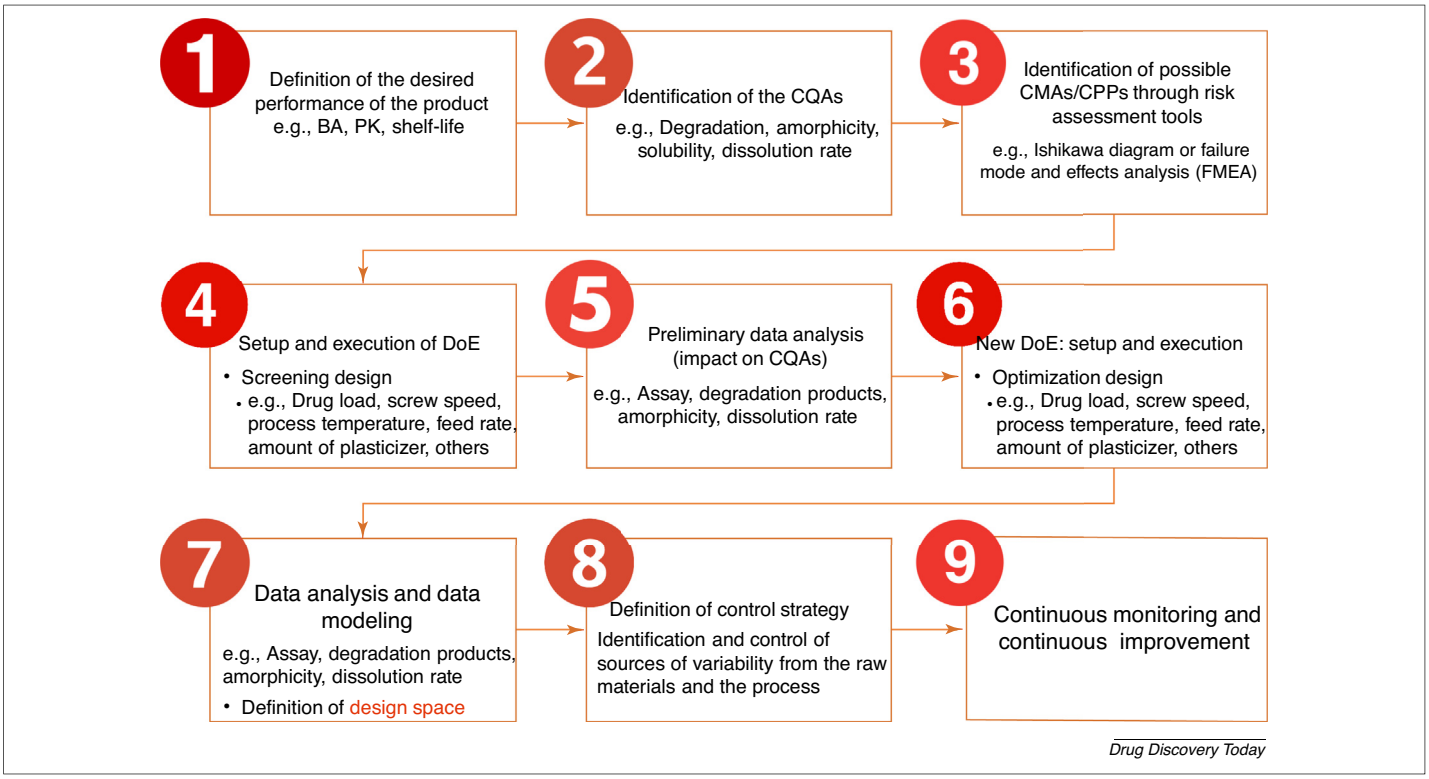

FIGURE 6

Nine-step quality by design (QbD) roadmap applied to hot-melt extrusion (HME): from the definition of QTPP to the product and process continuous monitoring and improvement. Abbreviations: QTPP, quality target product profile; BA, bioavailability; PK, pharmacokinetics; CQAs, critical quality attributes; CMAs, critical material attributes; CPPs, critical process parameters; DoE, design of experiments.

TABLE 2

REM example of an initial risk assessment of the manufacturing process for an ASD manufactured by HME; each CPP was qualitatively ranked as high, medium or low-risk level considering the probability of occurrence and the severity of the impact on the CQAs.

Risk estimation matrix (REM)

Process steps						Hot-melt extrusion							Milling		
Process parameters/ CQAs	Room Temperature and relative humidity	Blending Order of addition	Mixer speed	Blending time	Feed rate	Process temperature	Screw speed	Screw design	Residence time	Cooling Belt speed	Sieve size	Sieve speed	Storage Temperature and relative humidity
Assay	Low	Low	Low	Med	Med	High	High	Med	High	Low	Med	Med	Low
Content uniformity	Low	Low	Low	High	Med	Med	High	Med	Med	Low	Med	Med	Low
Dissolution	High	Low	Low	Low	High	High	High	High	High	Med	High	High	High
Degradation products	Low	Low	Low	Low	High	High	High	High	High	Low	Low	Med	Med

Abbreviations: High, high risk; Med, medium risk; Low, low risk; ASD, amorphous solid dispersion; HME, hot-melt extrusion; CPP, critical process parameter; CQAs, critical quality attributes.

risk considering the severity and the probability of occurrence of the impact on the CQAs. Parameters identified as high risk should be further evaluated through a DoE. The risk ranking was performed on the assumptions of a good manufacturing practice (GMP) environment and room conditions, in manufacturing and storage, and the use of conventional equipment in a pharmaceutical facility, such as bin blenders, twin-screw extruders and mills equipped with hammers or knives.

Since the establishment of the QbD initiative, one of the most useful tools for the identification of a design space is DoE. Indeed, DoE is the most effective approach to acquiring a good understanding of the process [163,170,175]. The adoption of statistical techniques based on desirability approaches and the evaluation of the optimization ability of statistical models has been widely used and has been shown to be crucial for a successful product development [176,177]. It is important to note that, in all the studies involving DoE and statistical analysis, the dissolution rate is the most commonly defined dependent variable, which confirms and emphasizes the importance of this response for ASDs [170,172]. In some cases, the physical stability was also included in the statistical analysis, using formulation and process as factors [178]. Typical QbD designs for pharmaceuticals were recently reviewed by Mishra *et al*. [166]. Moreover, a complete and practical review of DoE was published by Sandoz scientists, where the focus was current practices within the pharmaceutical industry, namely development strategies, typical experimental designs and modeling methodologies [179].

Another important tool of QbD is PAT. Applications of PAT comprise the identification of polymorphic forms, characterization of solid states (crystalline or amorphous), detection of impurities and degradation products, determination of water content, uniformity of drugs, among others, via on-line, in-line or at-line measurements of the CQAs [58,180,181]. This is still an emerging issue for HME, with new publications each month [182–185]. A review was published in 2017 in collaboration with AbbVie where the use of well-established and emerging PATs is assessed for the manufacturing of ASD by HME, with a focus on industrial manufacturing [186].

Design space of a HME product

HME fits well within QbD principles, namely defining a design space. For industries, the establishment of a design space is a real advantage, because it is not considered a regulatory change provided they work within it [29,170]. CPPs of HME processes can be readily determined, because the manufacturing at steady state allows multiple sequential testing with minimal material losses. The knowledge of the overall process goals, the aims of each unit operation (e.g., feeding, conveying, blending, kneading, melting) and their relationship should be carefully evaluated to build the design space [169].

Several examples of QbD strategies for HME products published by the pharmaceutical industry are available, for instance by ACG Pharma [96], Amneal [149], Ashland [187], Novartis and Genentech [154], Foster Delivery Sciences [188], BASF in collaboration with ThermoFisher Scientific [156], Dr Reddy's [189], Grünenthal [190], Boehringer-Ingelheim [191], Evonik [157], Nektar Therapeutics and Mallinckrodt [192,193], ThermoFisher Scientific [158], Merck [194], among others [195]. A Box-Behnken factorial DoE

approach was reported by Pawar *et al.* in which efavirenz was combined with Soluplus® or copovidone, in three drug loads. Solubility and dissolution rate were studied through the effect of variables like polymer ratio, screw speed and temperature, and the design space is provided [96]. The effect of HME process parameters on product performance of an amorphous nanosuspension was also studied by a Box-Behnken DoE [149]. In another study, a simplex centroid mixture design was applied to develop an optimized formulation of itraconazole processed by HME. Three different polymers were combined with the drug at 25% of drug load and, after modeling, the best formulation was determined [187]. Desai *et al.* studied the impact of CPPs on the downstream processing step, namely injection pressure and solidification temperature of a HME injection molding formulation. Risk assessment and other QbD concepts such as CQAs and CPPs were applied; however, the authors provide no statistical analysis [154]. Other statistical methods to reach a design space have also been described in the literature, such as mixture designs [191,195], central composite design [156,190], retrospective analysis [190], Plackett–Burman screening design [157], response surface design [157,193] and response surface fraction factorial design [158]. As noted by Debevec *et al.*, there is no uniform way of developing a design space for the pharmaceutical development of different dosage forms and regulatory guidance is still vague. Despite the fact that different strategies are acceptable, those must be based on sound science, risk management, adequate planning of experiences and statistical data analysis [179].

Regulatory evaluation of HME-based products

In this era of building QbD, the pharmaceutical industry is regulated and governed by several authorities and regulatory bodies. The ASDs are complex formulations, where science is vital to guarantee product quality, not only regarding degradation but also in what concerns polymer science, physicochemical and thermodynamic concepts, physical stability and process control. In this regard, possible questions and issues from the dossier reviewer's perspective can arise and are listed hereafter (Table 3). These questions should be taken into account not only during dossier compilation but also during product development.

The need for an ASD formulation, a complex composition, to achieve the quality target profile should be appropriately justified, and this should be performed through a patient-centric perspective: to improve BA, physical stability, decrease the drug burden or improve the overall safety profile of the drug product. The usage of appropriate biopharmaceutical tools is also of foremost importance for this type of formulation. Usually, dissolution tests are applied, but they need to be demonstrated as discriminative and capable of detecting small amounts of drug crystallization. It is recommended to complement dissolution with solid-state characterization, most commonly X-ray powder diffraction (XRPD), but DSC can also be applied as well as, more recently, Raman spectroscopy [74,99,170]. Owing to the high impact on drug release and BA, this should be assessed not only during formulation screening but throughout the whole product and process development, as well as in pre-stability and ICH stability studies.

The selection of critical excipients should also be appropriately justified, namely in what concerns the impact on the physical stability and chemical compatibility with the drug. Similarly, the container closure system needs to be evaluated through stability studies but also in use. Usually, a new shelf-life after opening HDPE bottles is defined, owing to the impact of moisture on product physical stability. Concerning CMAs, the drug and the excipients require extensive evaluation in terms of polymorphism, thermal behavior and hygroscopicity, but the impact of moisture should be particularly evaluated. Moisture causes the decrease of the overall blend T_g [196], which could lead to increased molecular mobility and eventually recrystallization. The batch upscale also needs to be carefully monitored and the end product fully characterized, owing to the high impact of process parameters on the ASD physicochemical properties. The product manufactured at the commercial scale must have the same performance as the one used in pivotal studies. Therefore, if the design space is established at the laboratory or pilot scale it should be verified at the commercial scale to assure quality performance throughout the product lifecycle.

A control strategy for the entire process, encompassing input material controls, process monitoring and controls, design spaces around individual or multiple unit operations, and/or final product specification should also be established. PAT tools can be incorporated into the control strategy for real-time monitoring and control of the process. If used, PATs need to be studied, demonstrated and validated for the intended purpose. For the CTD, detailed data on the ASD as an intermediate should be included in the drug product section and characterized almost as an end product. The extrusion process should also be considered within hold-time studies, for instance from extrusion to downstream processing and from processed extrudate to final blending.

In what concerns inactive ingredients, only the ones generally recognized as safe (GRAS) are listed in the FDA's inactive ingredient database, have a compendial monograph or are documented for human use at specific levels. To ensure that all new excipients are safe for use in humans, a comprehensive evaluation of pharmacology, including carcinogenicity and chronic toxicity, is mandatory [197]. This is especially relevant for HME-based formulations because the amounts of polymers are typically much higher than in conventional dosage forms, where they are used as binders or as film-forming agents in coatings. Finally, and common to other processes, all extruders used for pharmaceutical HME processes must also comply with the cleaning and validation requirements of the GMPs, and all surfaces that come in direct contact with the materials or finished product must be nonreactive, non-absorptive and nonadditive [198–200].

Case studies of recent approvals

In this section, the latest approvals of ASDs manufactured by HME are analyzed as case studies within the QbD paradigm.

Belsomra® (Merck, 2014)

Belsomra® was developed by Merck and was approved in 2014 in the USA [68], and also in Japan [201]. It is an ASD prepared by HME to maximize BA, as a BCS class II compound [62]. The team selected to extrude the compound with a pH-independent solubility polymer, copovidone [69], and to coat and pack in aluminum blisters, to protect from light and moisture. The product development followed full QbD principles, from the compound synthesis to the product development and manufacturing. In the drug synthe-

TABLE 3

Possible questions from the reviewer's perspective focused on ASD issues [199].

Topic	Issue	Comments
Product design and understanding	Justification of the need for ASD formulation to achieve QTPP targets	–
	Use of appropriate biopharmaceutics tools (e.g., discriminating dissolution methods) to screen formulations	Discriminating capability can be demonstrated by conducting dissolution on ASD formulation with spiked crystalline drug Absorption modeling can be considered to determine the extent of phase change that can cause clinical BA failure
	Justification for the selection of crucial excipients including physical and chemical compatibility: polymer/additives selection and justification	To be considered ■ Miscibility with drug ■ Phase behavior under heat and humidity stress: phase separation ■ Phase behavior during dissolution: supersaturation behavior ■ Process considerations: e.g., HME vs spray-drying Prototype formulation stability is not similar to excipient compatibility. Chemical compatibility should be carefully used
	Justification of container closure system choice proposed by the applicant	Prove adequate protection to assure adequate product performance throughout shelf life
	Stability data to guarantee that the drug product will be physically and chemically stable throughout the shelf life and in use	ICH stability conditions do not capture in use behavior. Demonstration of product performance under simulated in use condition is recommended ■ Induction seal broken; daily open and close ■ Potential transient exposure to high humidity (e.g., bathroom or kitchen storage, high humidity seasons) ■ Decreased or no moisture protection until the container is exhausted
	Physicochemical characterization of drug	e.g., Phase behavior of crystalline and amorphous forms, effect of humidity and heat stress
	Critical material attributes of drug	e.g., ■ Polymorphism ■ Crystalline vs amorphous behavior ■ Hygroscopicity ■ Thermal behavior (T_m and T_g) ■ Solubility ■ Impurities ■ Residual solvents
	Critical material attributes of excipients	e.g., ■ Polymers: T_m, T_g, hygroscopicity, MW, viscosity, effect of substitution, amphiphilic/nonamphiphilic ■ Surfactants: hydrophilic–lipophilic balance, peroxide/aldehyde levels
	Justification on drug-loading limit	Selected drug load should be well below the limit of failure
	Demonstration of scaleup to commercial scale Assurance that product manufactured at the commercial scale has the same performance as the one used in pivotal studies Verification of design space at a commercial scale when established at a lower scale	–
	Potential for continuous manufacturing	Including PATs implementation
Control strategy	Demonstrated and validated appropriate PAT methods for real-time product release	–
	Conventional methods for detecting crystallization during routine manufacture and lifecycle control (e.g., XRD, dissolution, Raman, DSC, microscopy)	Product development might benefit from more-advanced methods, e.g., spectroscopy (NMR, terahertz) Development of methods to detect crystallization should be done during product development. Method validation should demonstrate that it is suitable for use

TABLE 3 (*Continued*)

Topic	Issue	Comments
General regulatory considerations	ASD information, as an intermediate, should be included in the drug product section of eCTD	–
	Holding-time studies should be carefully performed and justified	–
	Date of drug product manufacture: recommended to be the date of ASD addition to the final drug product	–
	Size and shape constrictions for generic tablets and capsules	For the US market [200]
	Comply with the Inactive Ingredient Database limits (maximum potency per dosage unit)	Otherwise, toxicological studies are required. For the US market
Human use	Requirements for new excipients	A comprehensive evaluation of pharmacology, including carcinogenicity and chronic toxicity, is mandatory. Need to be recognized as GRAS
	Requirements for GMP manufacturing	Cleaning and validation requirements All surfaces that come in direct contact with the materials or the finished product must be nonreactive, non-absorptive and nonadditive

Abbreviations: ASD, amorphous solid dispersions; QTPP, quality target product profile; BA, bioavailability; HME, hot-melt extrusion; ICH, International Conference on Harmonization; Tm, melting temperature; Tg, glass transition temperature; MW, molecular weight; PATs, process analytical technologies; XRD, X-ray diffraction; DSC, differential scanning calorimetry; eCTD, electronic common technical document; GMP, good manufacturing practice; GRAS, generally recognized as safe.

sis, DoE and statistical analysis were applied for a complete understanding of the process, namely identification of QTPP and CQAs, risk assessment and DoE; to understand the impact of CMAs and CPPs on the product performance. Moreover, the design space was identified and the proposed ranges further confirmed (proven acceptable ranges, PARs) by worst-case-scenario experiments. Drug substance specifications, in most cases, were established based on multifactor DoE and design space. A complete control strategy was presented, with raw material specifications, in-process controls (IPCs) and release specification [202].

The development of the drug product was also based on QbD principles, and design spaces were proposed for several unit operations [202]. For instance, CQAs were defined through risk assessment and are listed as, among other things, content uniformity, assay, degradation products, physical form, stability and dissolution. The discriminating ability of the dissolution method was proven toward several CPPs. It is the same method and specification for all the strengths, and similarity between them was proven, indicating that the lower and the higher strengths have similar performance. Drug release, as one of the most important CQAs, was used as a response parameter to support the design space of the product. A multiple level C *in-vitro–in-vivo* correlation (IVIVC) model was developed to support the proposed dissolution acceptance criterion and even to establish IPCs [203]. This correlation was published, and the authors stated that a clear relationship between dissolution, disintegration and C_{max} exists [28,62]. The IVIVC was validated for C_{max} for specific dissolution time points and tablet disintegration time. Then, tablet hardness was linked to dissolution to provide adequate ranges, which allowed the establishment of a clinically relevant IPC. This study shed light on IVIVC as a complementary tool to QbD, namely to support the establishment of clinically relevant controls [62].

Viekirax®/Technivie® (AbbVie, 2015)

Viekirax® (EU)/Technivie® (USA) is a fixed-combination tablet, developed by AbbVie and approved in 2014 by the EMA and in 2015 by the FDA. All three drugs in the combination are individually converted into amorphous materials by HME to enhance their BA. Only then the individual extrudates are combined, tableted and coated [65]. Tablets are packed in aluminum blisters (USA) or PVC/PE/PCTFE–aluminum blisters (EU) for maximum water vapor and oxygen protection. The development focused on optimizing the three solid dispersions individually. During the first steps of formulation development, ombitasvir and paritaprevir solid dispersions were manufactured by spray-drying, but a solvent-free process was preferred. Moreover, *in vivo* studies comparing spray-drying to HME showed that C_{max} and AUC from the HME formulations were substantially higher. Ritonavir followed the path of Norvir®, keeping the same manufacturing process (HME) and extrudate composition [65]. During HME, the three drugs are converted from the crystalline to the amorphous state, with no recrystallization on storage [65,204,205].

There is not much available information on the development of this product. To our knowledge, there is no additional literature besides that published by the EMA and FDA during product review [65,204,205]. They applied risk assessments, and other QbD concepts such as QTPP and CQA definition, the study of CPPs and CMAs through DoE, data modeling and statistical analysis (no details available) [204]. A final risk assessment and a control strategy is referred for the control of drug synthesis and the manufacturing of the final product [65]. The release of the finished product includes typical parameters for an ASD, for instance degradation products, solid state form, water content and dissolution [65,204]. The discriminating power of the dissolution method was proven, and specification criteria thoroughly discussed between the applicant and the agency [204]. Although this method

does not meet sink conditions, it does provide sensitivity to crystallinity.

Venclyxto®/Venclexta® (AbbVie, 2016)

Venetoclax was developed by AbbVie in collaboration with Genentech and Roche and was approved as Venclyxto® in the EU and as Venclexta® in the USA, both in 2016. It is also manufactured by HME as a solid dispersion owing to the very poor water solubility of this compound [70]. Mixtures of drug and copovidone with surfactants were extruded to enhance BA [71]. It is available in HDPE bottles and unit-dose PVC/PE/PCTFE–aluminum foil blisters, which were demonstrated to provide adequate protection from oxygen and moisture to avoid chemical degradation or recrystallization of the product [70]. The development of this product also followed QbD principles, from the synthesis of the compound to the development of the drug product. A systematic approach was taken during the development of the compound: identification of the potential drug CQAs that could affect drug product QTPP, identification of CMAs and CPPs through prior knowledge, DoE and use of process understanding and risk management to establish the control strategy. The development of the manufacturing process was based on a combination of univariate studies, DoE and kinetic modeling, but no design space has been claimed by the applicant [70,206].

The focus of formulation development was set on the BA, storage stability and manufacturability. The development of the finished product contains QbD elements too, similar to those previously described for the drug, with no request for design space approval. The development was based on experience with similar products, published literature, DoE and material characterization. It ends with the updated risk assessment, where low residual risks were rated for all parameters, and the control strategy, where CPPs and IPCs for the extrusion were determined to ensure a homogeneous blend and adequate dissolution. In addition, target parameters and PARs were specified for each CPP [70]. The release specification includes appropriate tests for an ASD, including water content, dissolution and degradation products [70,207], from which dissolution and water content were considered the most crucial. The dissolution recommended for quality control (QC) is a reciprocating cylinder (USP apparatus 3) with 250 ml phosphate buffer pH 6.8 with 0.4% sodium dodecyl sulfate, considered biorelevant. This method has demonstrated a discriminating capacity to changes in the crystalline venetoclax content of tablets, and this is why solid-state analysis of venetoclax tablets is not performed [70]. After discussion with the agency, a strength-dependent multipoint dissolution acceptance criteria was established [207]. The three strengths have different dissolution profiles because the release is governed by erosion; however, available *in vivo* studies did not indicate a relevant difference in BA [70]. To understand the mechanisms of drug absorption in humans, a physiologically based pharmacokinetic (PBPK) model was developed by AbbVie, verified with fed and fasted clinical studies, as well as clinical drug interaction studies [208]. This study demonstrated how innovative tools, such as PKPB models, might be applied and be part of product development, in a clear trend to turn the development of pharmaceutical products to be more and more patient-centered.

Maviret®/Mavyret® (AbbVie, 2017)

The latest approval of a HME-based ASD, to our knowledge, is a fixed-drug-combination of glecaprevir and pibrentasvir, also developed by AbbVie, and approved under the names Maviret® by the EMA or Mavyret® by the FDA. Both drugs in the combination are poorly water-soluble, and they are also individually formulated as ASDs to increase solubility and to enhance BA [72]. The individual extrudates are milled, compressed into bilayer tablets and coated with an esthetic film. Tablets are packed into blister cards of PVC/PE/PCTFE–aluminum to protect from moisture. There is not much available information on the development of this product. To our knowledge, there is no additional literature besides that published by the EMA and FDA during product review [72,209,210]. The synthesis process of both drugs is well described and controlled, including CPPs with proper ranges to ensure a product with consistent quality. An adequate control strategy was also provided to authorities [72] but a complete QbD study was not mentioned.

In what concerns the formulation development, the focus was the enhancement of BA and physical stability. It started with the development of the individual solid dispersions as first-in-human tablets, used in early phases of clinical development [210]. A full QbD approach was taken to develop the tablet formulation and manufacturing process, although the applicant did not claim a design space. The QTPP was defined, as well as the product CQAs. Then, systematic evaluation and optimization of the manufacturing process, namely the relationship between CMAs and CPPs with the product performance, were carried out using DoE, statistical analysis and mathematical modeling. For instance, several particle sizes of both drugs were evaluated and an appropriate specification was set. The control strategy was then defined and the risk assessment updated to demonstrate that the risks were mitigated. The release specification includes appropriate tests for an ASD, like degradation products, water content and dissolution [72]. The dissolution method demonstrated the capacity of discriminating specific changes in formulation or process parameters. The applicant used a two-stage numerical deconvolution approach to establish an IVIVC, but it was not successful, although a relationship between *in vitro* and *in vivo* data was noticed. A two-point specification was set for both drugs owing to the slow release from tablets [209]. It is not mentioned whether the dissolution method can detect drug crystallinity, but full amorphicity is controlled after extrusion [72]. In addition, the effect of different tablet manipulations (namely splitting, crushing or grinding) on the BA of the two compounds was assessed in a Phase I clinical trial. Splitting tablets demonstrated no relevant impact on BA, but crushing or grinding is not recommended [211]. This study is also part of QbD, because it enhances the knowledge on the product behavior, apart from providing guidance on adequate administration to patients.

Concluding remarks and future perspectives

HME is not yet a common technique to manufacture new DDS, and few products have reached the market so far. This trend is clearly being shifted as more and more HME products are finally getting into the pipeline of pharmaceutical companies, which is also translated by the high number of publications found in this field. Technical and scientific challenges of amorphous forms and the intrinsic complexity of these developments request the collaboration of specialists from industry and academia. This reflects

the science and the dedication needed for successful ASD development. Moreover, the increasing number of recent publications from pharma is high, demonstrating the stronger trend in sharing work and scientific achievements.

Other techniques have been used in the industrial setting for the amorphization of practically insoluble drugs, including spray-drying, freeze-drying and supercritical fluid drying. However, HME is the only solvent-free technology, easily upscalable and fast, which allows a continuous process and with a small footprint. HME also has some disadvantages: it works under high temperatures (which can lead to the rejection of thermolabile compounds); it requires downstream processing most of the time; and the input of a large amount of energy is necessary. Moreover, the number of polymers with thermoplastic characteristics approved for pharmaceutical application is admittedly low and still presents unique challenges as a result of the metastable nature of ASDs. Specifically for ASDs, the impact of process parameters on the product quality is crucial, and small variations in the feeding rate, local temperature, screw speed, resident time or cooling rate can lead to an end product with slightly different internal microstructure. As we are referring to ASDs, this could lead to an entire batch failure owing to a dramatic change of the dissolution behavior. Indeed, a complete understanding of the complex relationship interplay between process and product parameters must be completely dominated to ensure quality and consistency. As an attractive alternative to other processes, the interest in HME has rapidly grown and several companies are now specialized in HME as a new delivery technology and have developed a significant (and recent) amount of intellectual property. This is, in fact, one of the issues related to widespread product development using HME, because the number of patented technology platforms is rising very fast and specific uses might be blocked.

The aim of this work was to look at how to develop and submit new products to regulatory authorities. There is no established approach, even after decades of working with amorphous forms. Based on a thorough literature research focused on reports from the pharmaceutical industry and the experience of our group, a systematic step-by-step approach for the development of HME products was proposed. Common thermodynamic assessments were reviewed and illustrated with proven application examples from the industry. However, further developments are still expected in the next couple of years. The success of future developments lies in not giving up the research on the applicability of thermodynamics and other predictive methods as replacements for the current strategies. Useful and practical methods, rather than heavy and unfeasible ones, able to rapidly guide formulation scientists toward the right formulation will certainly be beneficial.

As a core in product development, the QbD paradigm applied to HME has been discussed, including steps and tools for its implementation and a risk assessment based on REM that can support regulatory dossiers. Moreover, possible questions from reviewers were listed, which reflect the technical and scientific specificities of this type of formulation. HME has a unique adaptability to QbD and PAT tools, recognized by the FDA. The construction of design spaces for HME products was also reviewed and supported by case studies of the latest approvals within the QbD paradigm. The usefulness of design space in the pharmaceutical industry will certainly lead to further research and new publications, because there is yet no uniform method. New thoughts, discussions and guidance from regulatory agencies in what concerns expectations on design space submissions would be valuable for formulation scientists.

The QbD philosophy is considered very useful for pharmaceutical development, and the primary proof is their application by all the recent approvals discussed in this paper. In all the dossiers, QbD elements and steps as the definition of QTPP, identification of CQAs, risk assessment for identification of crucial parameters or attributes, process and product understanding by DoE, data analysis and modeling were carefully applied throughout product development. In any case, the developments are more and more science-based, as requested by the QbD paradigm, and development decisions, the definition of controls, specifications and even IPCs are more patient-centered and focused on what is clinically relevant. HME will continue to be explored and investigated because simple formulations can be used to solve complex delivery issues. Moreover, because lipophilicity is the trend of new therapeutic compounds, the use of enabling formulations will be highly sought in the forthcoming years. HME will undoubtedly be a leading technology in this new paradigm, as a novel solution to poor BA and drug delivery through innovative platforms.

Conflicts of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter.

Acknowledgments

This work was supported by Bluepharma and by the Fundação para a Ciência e Tecnologia (FCT), grant no. PD/BDE/135149/2017. Figures 1, 2, 3, 4 and 5 were built based on templates provided by PresentationGO.com. Thanks to Branca Silva for our useful discussions on risk assessment methodologies. The authors also thank the Faculty of Pharmacy, University of Coimbra, for financial support.

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