Chapter 18
Melt Extrusion: A Commercial Perception to Practicality

Lessons Learned from Meltrex® Technology

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Abstract Over the past two decades, Meltrex® has evolved from being a novel processing technique into a comprehensive manufacturing technology. This chapter discusses the successful application of Meltrex® in the commercial development of delivery systems for varied drugs such as lopinavir (Kaletra®), ritonavir (Norvir®), ibuprofen, and verapamil hydrochloride (Isoptin®). Besides the commercial applications, Meltrex® can be successfully applied in design of solid dispersions (bioavailability enhancement of poorly soluble drugs), alter or control dissolution profiles (sustained release), reduced dosing frequency, deter substance abuse, improve safety, and efficacy of drugs. Moreover, continuous processing, rigorous and comprehensive regulatory documentation, and use of generally regarded as safe (GRAS) material are some of the striking features which make Meltrex® a popular drug delivery technology.

18.1 Introduction

Improving solubility, rate of dissolution, and hence the absorption and bioavailability of newly discovered drugs remains a challenging task ahead of the current research- and innovation-driven pharmaceutical industry. A considerable portion of the new molecular entities (NMEs) discovered today have low aqueous solubility and this portion may be increasing with the advent of combinatorial chemistry, progress in synthetic chemistry, and high throughput methods in drug discovery.

Currently, most pharmaceutical organizations observe a rapid decline in the sales value of their respective key products following patent expiry and competition from generic manufacturers. Introduction of new formulations of out-of-patent molecules

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M. A. Repka et al. (eds.), *Melt Extrusion,*
AAPS Advances in the Pharmaceutical Sciences Series 9,
DOI 10.1007/978-1-4614-8432-5_18, © American Association of Pharmaceutical Scientists 2013

with significant improvement in their pharmacokinetic profiles remains an important strategy to benefit patients largely.

Although, solubilization approaches are available, the challenge exists in incorporating them in an appropriate dosage form due to issues with reproducibility, scale-up, physical and chemical stability of the drug, and excipients used for formulation, in particular when solid dispersion or amorphous embeddings are used.

Melt extrusion, a thermally intensive process of converting a thermoplastic raw material into a product of defined shape, offers one possible solution (Crowley et al. 2007; Repka et al. 2008). Melt extrusion has been successfully applied as a solubility enhancement technique for poorly soluble drugs (Lakshman et al. 2008; Tho et al. 2010; Feng et al. 2011; Liu et al. 2012; Sakurai et al. 2012). Solubilization in the melt extrusion process occurs through dispersion of a poorly soluble drug(s) in a polymeric carrier matrix.

Over the past 15 years, several products have been successfully formulated through melt extrusion technology, Isoptin® SRE-240, fast-acting ibuprofen, Norvir®, and Kaletra® are examples of successfully developed tablet formulations using the proprietary Meltrex® technology. Abbott GmbH & Co. KG has adapted and developed Meltrex® (proprietary melt extrusion-based technology) into a process for the production of pharmaceuticals, which can meet the industry needs for both enhanced bioavailability of NMEs and improved formulations of existing products.

Kaletra®, containing the anti-HIV protease inhibitors lopinavir and ritonavir, is the first coformulated pharmaceutical composition to be successfully tableted using Meltrex® technology. More importantly from a therapeutic perspective, in comparison with the soft gelatin capsule (SGC) formulation of Kaletra®, Meltrex® tablets require fewer dose forms to be taken each day, can be stored at room temperature (SGC needs to be refrigerated), and do not need to be taken with food. The melt extrusion tablet formulation of Kaletra® represents a unique example of patient-centric HIV therapy.

18.2 Melt Extrusion: A Solid Dispersion Technique

Melt extrusion is a methodology wherein drug(s) are dispersed in a polymeric (or lipid) carrier matrix, thereby forming a solid dispersion (Shah et al. 2012). As defined by Chiou and Riegelman, a solid dispersion is a dispersion of one or more active pharmaceutical ingredient (API) in an inert carrier in the solid state, prepared either by melting, solvent, or the combined melting–solvent method. They present a classification of solid dispersions as eutectic mixtures, solid solutions, and glass solutions based on the physical state of the drug and the carrier, respectively (Chiou and Riegelman 1971).

The solid dispersions prepared by melt extrusion-based processing can be classified as crystalline solid dispersions, amorphous solid dispersions, and solid solutions (a subgroup of amorphous solid dispersions; Serajuddin 1999; Leuner and Dressman 2000; Janssens and Van den Mooter 2009; Shah et al. 2012).

Although pharmaceutical solid dispersions are prepared with an aim to enhance the solubility and hence bioavailability of drugs, equal importance should be given to studies focused at understanding the physical form of drug in the carrier matrix (recrystallization behavior, stability, etc.).

18.3 The Meltrex® Technology

Meltrex® technology has been developed with the specific aim to combine the preparation of solid dispersions with defined controlled-release characteristics in a single manufacturing process (Breitenbach 2002, 2006; Breitenbach and Lewis 2008). The drug can ultimately exist in either an amorphous or a crystalline form. Meltrex® technology can be used to formulate crystalline drug substances into solid dispersions independent of their polymorphic form or the particle-size distribution.

Meltrex® represents a process free of volatile solvents for the production of pharmaceuticals, which can meet the industry needs for both enhanced bioavailability of NMEs and improved formulations of existing products. In essence, rather than using polymers simply as binders or excipients, as in the conventional tableting process, Meltrex® uses their intrinsic matrix-forming properties as a fundamental part of a drug delivery system (Figs. 18.1 and 18.2).

In the Meltrex® process, the drug substance itself (or as a premix, depending for example on the flow characteristics of the drug) together with a pharmaceutically acceptable polymer and any additional excipients (if required) are fed continuously through a loss-in-weight hopper system into the twin-screw extruder. The ingredients are thoroughly mixed by the corotating screws where most of the energy input is provided by the shear forces of the corotating screws. In addition, the chambers can be heated briefly during the mixing process.

The heating step softens the polymer to enhance mixing and subsequent flow through the slit or nozzle; often the drug itself may act as a plasticizer, which further reduces the need for high temperatures during processing. The actual temperature can depend on a variety of factors such as the thermal stability of the drug, the thermoplasticity of polymer being used, and the pharmacokinetic profile that is required for the final product.

Typical operating temperatures are at around 90–120 °C but, for example, peptides have been successfully extruded at much lower temperatures. Extrusion through a slit creates a ribbon that passes through two calendar rollers, which can result in tablets either in a variety of shapes and sizes or in a thin film (Xellex™). The tablets require a minimum of further processing and can be coated for cosmetic or taste-masking purposes and the films can be used as a coating or, for example, for buccal administration. Extruding through a nozzle produces spaghetti-like strands, which can be cut into pellets for filling into capsules. Granules can also be produced from the extruder and these can then be milled and compressed, often directly, into conventional tablets. As the drug substance and the polymer are thoroughly mixed during the extrusion process, the release profile is an intrinsic property of the resulting formulation and is not dependent on, for example, any additional coating.

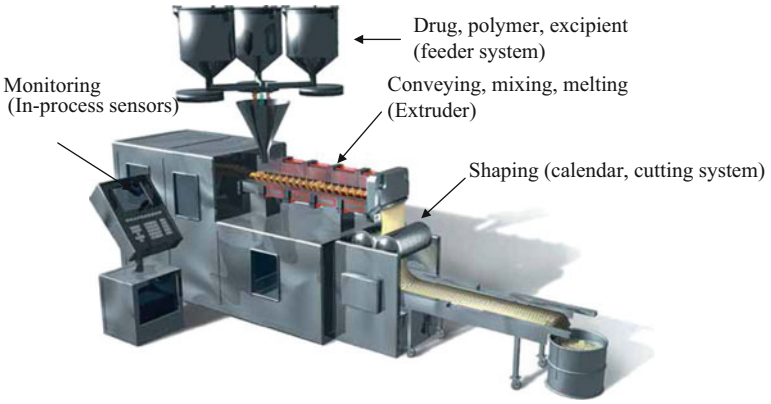

Fig. 18.1 Schematic representation of a typical pharmaceutical twin-screw extruder that represents the core element of the Meltrex® manufacturing process. The basic components of this equipment are the hopper, barrels, screws, kneaders, dies, and a kneading device. (Adapted with permission from Breitenbach (2002))

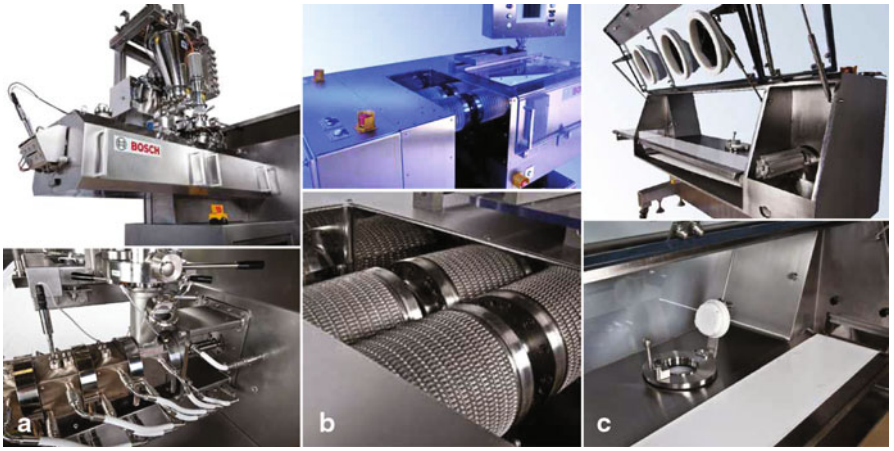

Fig. 18.2 **a–c** Depiction of the individual components of a BOSCH Hot Melt Extrusion Line WCF, BPK, BCK (extruder, calendar, cooling tunnel). **a** BOSCH pharma extruder WCF 0040. **b** BOSCH pharma calendar BPK0050. **c** BOSCH pharma cooling tunnel BCK0050. (Used with permission of BOSCH (2012))

Often the resulting formulation gives a clear, transparent tablet. Solid dispersions produced by processes like melt extrusion may have the additional advantage of being able to combine both enhanced bioavailability and a specific controlled-release profile in the same formulation. The drug load for solid dispersion formulations is typically in the range of 30–60 %, depending on the solubility of the drug in the polymer. Clearly, it is advisable to avoid a supersaturated product, which may then recrystallize and real-time stability data results demonstrate with a variety of different

compounds that no crystal formation in the solid dispersion formulations occurred for more than ten years in some cases.

Following are the engineering or built-in design advantages of the twin-screw extruder:

1. *Short-residence time application to thermolabile substanc*es: The average residence time for drug polymer mix in the twin-screw extruder is around 2 min. The extrusion process moves the molten mass continuously through the extrusion channel, thereby avoiding heat stress on the drug-polymeric matrix blend. This time duration is sufficient enough to ensure the plasticity of extruded material and simultaneously also avoid any major decomposition or unwarranted changes in the physicochemical properties of melt-extruded material. Several drugs and drug carriers are thermally unstable and undergo major physical and even chemical changes on prolonged exposure to high temperatures required to melt or fuse the material.
2. *Shaping*: Another core element of the Meltrex® process is the ability to shape the molten strand that is expelled from the extruder. The mass is forced through two rollers, which can then produce tablets of various shapes or a thin film (Xellex®). The process as such can also produce granules for subsequent milling and compression into conventional tablets. The final drug release profile is an intrinsic property of the extrudate and this profile remains unhampered during milling, compression, or any subsequent downstream processing step and the extrudate can be simply used for the manufacture of a specific delivery system.
3. *Self-wiping screws*: The root of the self-wiping screw, wipes on the shaft of adjacent screw, thereby ensuring near-complete emptying of the extruder at the end of process. Also, this built-in design makes the extruder amenable to Good Manufacturing Practice operations wherein cleaning and sanitization can be easily performed at the end of a batch process.
4. *Versatility*: The extruder is designed with maximum versatility. Die plates can be changed to alter the configuration and final form of the extruded material. In addition, the rate of extrusion and mixing action could be easily controlled. These features allow versatile formulations to be processed on a single machine, thereby optimizing equipment utilization.

A further advantage resulting from the formation of solid dispersions with technologies like the Meltrex® technology is that it may produce stable amorphous final dosage forms, thus eliminating many of the formulation and bioavailability problems associated with drug compounds, which exhibit several polymorphic forms.

18.4 Overview of Kaletra® Tablets

Highly active antiretroviral therapy (HAART) is an intensive treatment regimen for HIV that employs a combination of antiretroviral drugs (protease inhibitor and nucleoside analogue; von Hentig 2007). Although HAART is an effective therapy, it is

limited by the patient-unfriendly treatment regimen. The treatment regimen requires frequent administration of several pills. Further, the pills need to be administered around mealtimes. The fact that some of the drugs require refrigeration further reduces the convenience of a regimen. The problem is further compounded in the HIV-affected developing parts of world where maintaining a cold chain for shipment and refrigerated storage during subsequent use of the medication is a major challenge.

A recent development, which illustrates the potential benefits achievable by solid dispersions, has been the reformulation of the leading protease inhibitor drug combination product, Kaletra® as part of Abbott Laboratories' on-going product improvement strategy (Breitenbach 2006). Kaletra® is a preparation of two protease inhibitors, lopinavir and ritonavir; it is the only coformulated protease inhibitor combination dosage form available in the market. (Cvetkovic and Goa 2003; Oldfield and Plosker 2006; von Hentig 2007; Croxtall and Perry 2010). The improvement of pharmacokinetic properties of lopinavir is attributed to the inhibitory effect of ritonavir on cytochrome P450 enzyme (primarily responsible for the metabolism of lopinavir).

Active ingredients, lopinavir and ritonavir, are poorly soluble in water and have negligible absorption from the gut when administered as unformulated solids. The first-marketed Kaletra® product was a soft-gel capsule (SGC) formulation, each capsule containing 133 mg lopinavir/33 mg ritonavir, with an adult regimen of 6 capsules per day.

The new Kaletra® tablets, made using Abbott's Meltrex® technology, contain 200 mg lopinavir/50 mg ritonavir per tablet in a "solid solution" with a resulting adult regimen of only 4 tablets per day. Abbott received US Food and Drug Administration fast-track approval of Kaletra® tablets for marketing in the USA in October 2005, followed by EU approval in July 2006.

The new Kaletra® tablets not only reduce the daily pill burden (6 SGC vs. 4 tablets), but also provide several other benefits. The newly developed Kaletra® tablets did not require refrigeration and could be stored at ambient temperature. Further, the tablets did not require administration around mealtime, thereby providing a more flexible medication schedule. Overall, the melt-extruded formulation significantly improves HIV therapy management as demonstrated by providing reduced dosage frequency (4 tablets vs. 6 SGCs), flexible regimen (independent of mealtime) and ambient temperature storage of the tablets (Fig. 18.3).

18.5 The Kaletra® Tablet: Patient Benefit

Introduction of the Kaletra® Meltrex® tablet formulation reduced the daily pill count from 6 SGCs per day to 4 tablets per day. Meltrex® tablets could be stored at room temperature (SGC needs to be refrigerated). Unlike the SGC, the tablet contains nonanimal-sourced excipients and does not use unsaturated fatty acids as formulation excipients. Further, the Meltrex® tablet need not to be taken with food and provides

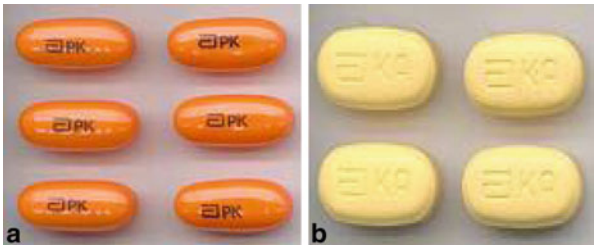

Fig. 18.3 An illustration of Kaletra® Meltrex® tablets and the original softgel capsules. **a** 6 Softgel capsules. **b** 4 Kaletra® Meltrex® tablets. (Used with permission from AbbVie Deutschland GmbH & Co. (2013))

consistent plasma levels of both drugs on a day-to-day basis independent of the varying meal conditions. Lower variability of lopinavir levels compared with those with the SGC.

In addition, it was demonstrated that the Meltrex® tablets were bioequivalent to the preexisting SGC formulation (Klein et al. 2007). Bioavailability of the melt-extruded tablet formulation of Kaletra® was assessed in three studies wherein tablet formulations of lopinavir/ritonavir at 800/200 mg or 400/100 mg under different meal conditions were compared with equal doses of the SGC after a moderate–fat meal. The tablet was found to be bioequivalent to the SGC after a moderate–fat meal based on the areas under the concentration-time curve (Fig. 18.4). Overall, the tablet formulation resulted in consistent plasma concentrations of lopinavir independent of the food intake, providing better therapeutic control.

18.6 Application of Meltrex® Technique in Development of Other Pharmaceutical Formulations

In addition to Kaletra®, Abbott has also developed a sustained release formulation of verapamil hydrochloride in cellulose ether matrix (Isoptin® SR-E 240 mg) that was the first directly shaped melt extrusion product on the market, as well as a fast-onset ibuprofen system (Andrews et al. 2010). Also, in 2010 Abbott announced that the US FDA approved a new thermally stable tablet formulation of the protease inhibitor Norvir® (ritonavir). This new formulation does not require refrigeration and can be stored at room temperature making it more convenient for patients.

Ibuprofen is known to be poorly soluble in aqueous acidic media. Though ibuprofen is completely absorbed upon oral administration (nearly 100 % bioavailability), the onset of absorption depends mainly on its dissolution and hence the type of formulation being administered. Meltrex® has been successfully applied to develop fast-onset ibuprofen, wherein ibuprofen is formulated as a solid dispersion in hydrophilic polymer matrix of polyvinyl pyrrolidone (PVP; Klueglich et al. 2005). The melt-extruded material is finally formulated as a film-coated tablet wherein the drug release (ibuprofen release) is dependent on the disintegration time of the tablet and the dissolution of the polymer and is independent of the solubility of ibuprofen. Such a formulation modification imparts fast-release properties to ibuprofen.

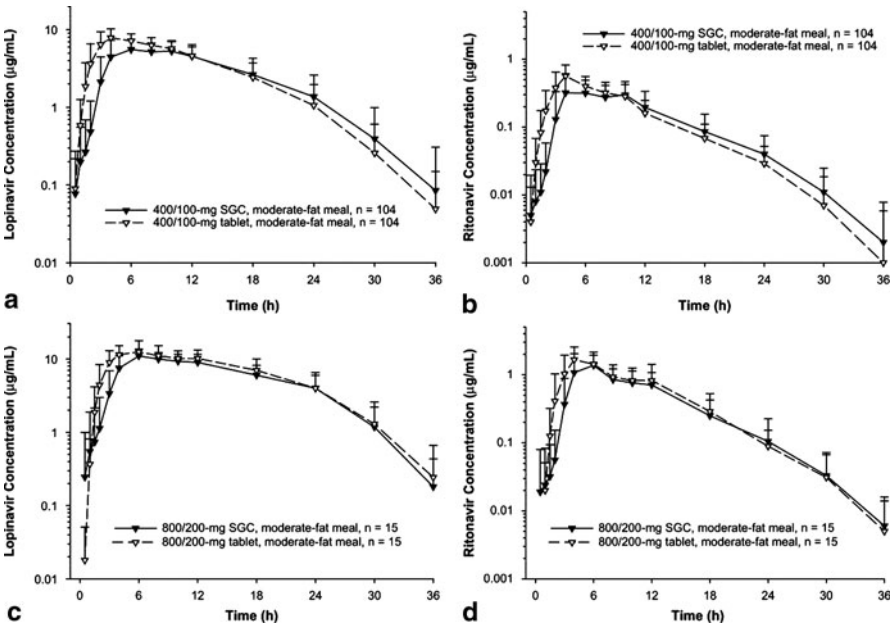

Fig. 18.4 The average ± SD concentrations of lopinavir and ritonavir after SGC (▼) or tablet (▽) administration of a single lopinavir/ritonavir dose of 400/100 mg with a moderate–fat breakfast [lopinavir (**a**) and ritonavir (**b**)] or 800/200 mg with a moderate–fat breakfast [lopinavir (**c**) and ritonavir (**d**)]. (Used with permission from Klein et al. (2007))

As shown in Fig. 18.5, under fasting conditions, ibuprofen lysinate and the novel ibuprofen extrudate tablet are bioequivalent on the basis of area under curve (AUC), C_{max}, and t_{max}. The pharmacokinetic profile of the novel extrudate tablet is different from that of regular ibuprofen under fasting conditions, with the C_{max} for extrudate tablet being approximately 20 % higher and t_{max} almost 1 h earlier than that for regular ibuprofen. The average total exposure as determined by AUC is almost identical though. Thus, although the extent of ibuprofen absorption is equivalent for the novel extrudate and regular ibuprofen, the rate of absorption is much faster for the novel extrudate (C_{max} and t_{max}). In conclusion, the pharmacokinetic profile of novel ibuprofen extrudate formulation is similar to ibuprofen lysinate and it is more rapidly available in plasma than regular ibuprofen (fast onset of action).

Meltrex® has been applied to verapamil hydrochloride, a marketed antihypertensive, and antianginal drug which can interact with alcohol. During extrusion, verapamil hydrochloride gets dispersed in the polymer melt (similar to those of ibuprofen and lopinavir described in the previous paragraphs) and the melt is subsequently shaped in the form of a tablet.

Roth et al. determined the influence of ethanol on the in vitro rate of release of marketed verapamil hydrochloride (240 mg) Meltrex® (Isoptin SR-E) and three marketed verapamil hydrochloride (240 mg) sustained-release (SR) formulations (Roth et al. 2009). Dissolution was tested under standardized conditions, with mediums

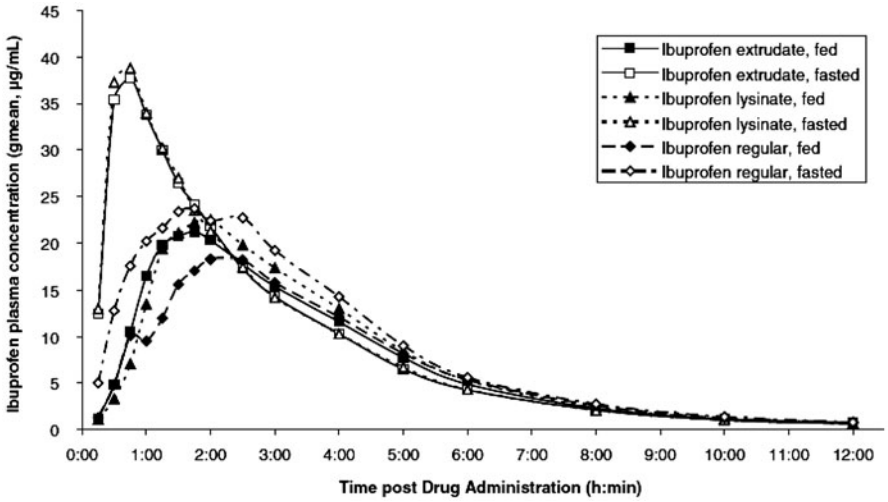

Fig. 18.5 Geometric mean ibuprofen plasma concentrations following single oral administration of a 400-mg ibuprofen extrudate (*square*), lysinate (*triangle*), and regular (*diamond*) tablet under fed (*filled*) and fasted (*open*) conditions, respectively. (Used with permission from Klueglich et al. (2005))

containing ethanol concentrations of 0, 5, 20, and 40 %. The dissolution profiles for verapamil hydrochloride Meltrex® showed no differences between 5 and 40 % ethanol vs. 0 % ethanol ($P > 0.05$). The mean dissolution percentage (%) was identical at 1 h (19 %) in 0 % vs. 40 % ethanol. In contrast, the three verapamil SR formulations showed significant increases in dissolution in 20 and 40 % ethanol versus 0 % ethanol ($P < 0.001$). An initial rapid release (within 2 h) was observed in 20 and 40 % ethanol, with a mean dissolution of 99 % (range 73–107 %). Therefore, unlike the three SR verapamil formulations tested, verapamil Meltrex® was found to be resistant to in vitro dose dumping when combined with readily accessible ethanol concentrations. The aim of their investigation was to determine the influence of ethanol on the in vitro release rate of verapamil hydrochloride from Meltrex® melt-extruded tablets (Form A) in contrast to three other direct compressed verapamil hydrochloride sustained release formulations (Forms B–D; Fig. 18.6).

18.7 Summary and Future Perspective

Over the years, Kaletra® melt-extruded tablets have become an important treatment option for patients with HIV. The application of Meltrex® technology has led to the reformulation of the product into a solid preparation that has significantly improved the convenience of Kaltera® treatment for patients with HIV. Application of the Meltrex® technology led to the overall product improvement (room temperature storage, reduction of pill count, dose schedule independent of meals, etc.) of

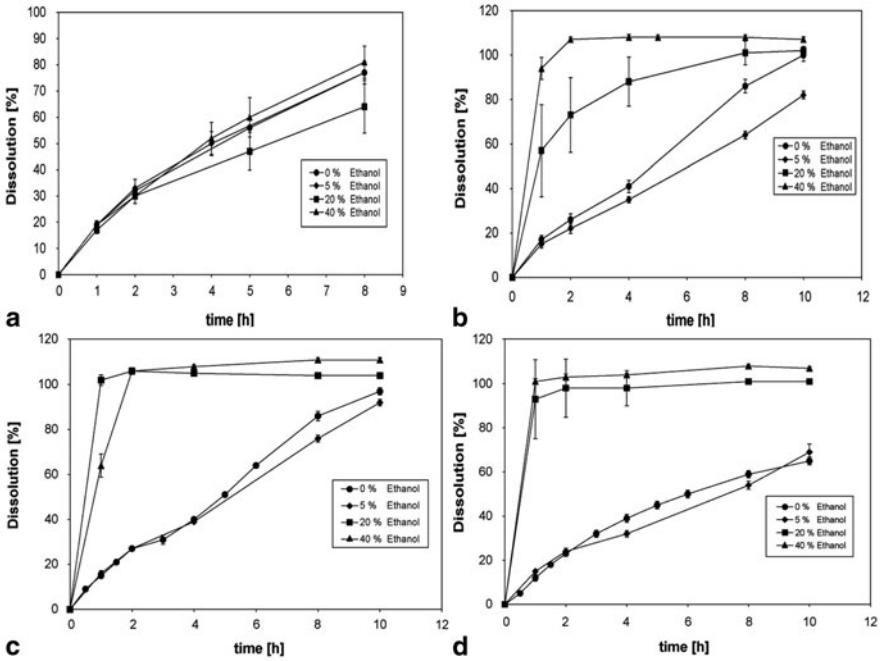

Fig. 18.6 Dissolution profiles (mean dissolution % [± SD]) of verapamil hydrochloride release from Form A (Meltrex®) (**a**), Form B (SR) (**b**), Form C (SR) (**c**), and Form D (SR) (**d**) over time (h), with increasing ethanol concentrations. (Used with permission from Roth et al. (2009))

Kaletra®. In addition, the Meltrex® technology has also been successfully applied to other drug formulations (ibuprofen and verapamil hydrochloride).

Taken together, Meltrex® is a highly efficient manufacturing technology that can be successfully applied for processing poorly soluble drugs as solid dispersion and can also be used to alter and control dissolution profiles of drugs. Meltrex® can be applied to a plethora of pharmaceutical systems with varied benefits such as reduced frequency of daily dosing, aid to deter substance abuse (e.g., opoid analgesics), improve safety, and provide sustained release profile. Meltrex®-based products have been approved in both the EU and USA. Moreover, Meltrex® has steadily evolved from an engineering technology into a comprehensive manufacturing platform amenable to current regulatory guidelines. Finally, since all the materials (polymers, processing aids, etc.) used in melt extrusion in general are pharmaceutically acceptable (GRAS approved), several existing formulations (already marketed) will undergo modification and develop into more efficient dosage forms to be approved in the near future.

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