Chapter 10
Extrusion: An Enabling Technology for Controlled-Release Hydrophilic Matrix Systems

Divya Tewari and Thomas Dürig

10.1 Introduction

The use of hydrophilic polymers in controlled-release matrix tablets dates back to the 1960s. An early example is the work of Lapidus and Lordi who reviewed factors affecting the release of water-soluble drugs from a hydrophilic matrix system [1]. However, the widespread commercial implementation of polymers like high molecular weight HPMC type 2208 for controlled release did not occur until the mid-1980s and can be said to have reached a peak in 1990s when a large number of hydrophilic matrix-based blockbuster drugs were launched in the United States and in Europe. Some examples include metformin HCl 500 and 750 mg extended-release tablets (Glucophage XR, Bristol-Myers Squibb), amoxicillin/clavulanic acid 1,000/62.5 mg extended-release tablets (Augmentin XR, GlaxoSmithkline), clarithromycin 500 mg extended-release tablets (Biaxin XL, AbbVie), divalproex sodium 250 and 500 mg tablets (Depakote ER, AbbVie), buproprion HCl 150 and 300 mg tablets (Wellbutrin SR, GlaxoSmithkline), zileuton 600 mg extended-release tablets (Zyflo CR, Cornestone), paroxetine HCl 12.5 and 25 mg extended-release tablets (Paxil CR, GlaxoSmithkline), and zolpidem tartrate 6.25 and 12.5 mg extended-release tablets (Ambien CR, Sanofi-Aventis). While other technology platforms such as coated multi-particulates (membrane-reservoir systems) and oral osmotic pump systems have also found commercial implementation, hydrophilic

D. Tewari, M.S., M. Pharm. (✉)
Manager, Global Pharmaceutical R&D and Technical Services, Ashland Specialty Ingredients, 500 Hercules Road, Wilmington, DE 19808, USA
e-mail: dtewari@ashland.com

T. Dürig, Ph.D.
Sr. Director, Global Pharmaceutical and Nutrition Specialties R&D, Ashland Specialty Ingredients, 500 Hercules Road, Wilmington, DE, USA

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matrix systems are today a dominant controlled-release technology platform. This is largely due to their decades-long proven safety and efficacy record and being amenable to commercial processing and manufacturing unit processes. In recent years, advances have been made in hydrophilic matrix polymers to provide directly compressible HPMC 2208 grades such as Benecel™ HPMC PH DC and a broad range of viscosity grades such as Benecel™ HPMC K250 PH PRM, K750 PH PRM, and K1500 PH PRM.

Due to the changing needs of new compounds and therapeutic regimes the drug delivery limitations of conventional controlled-release dosage forms are becoming increasingly common. This has required the development and introduction of new approaches to hydrophilic matrix formulation and processing to enable the delivery and commercialization of new compounds. In this chapter, we describe how the use of twin-screw extrusion combined with new hydrophilic matrix formulation approaches can provide for the controlled delivery of challenging compounds.

10.2 Limitations of Hydrophilic Matrix Systems and Approaches to Overcome the Limitations

Although widely used commercially, hydrophilic matrix systems have some well-known limitations. Amongst them is the ability to accommodate and control the release of large doses of highly soluble drugs.

Typical drug loads for wet granulated, dry granulated, or directly compressed tablets are usually 50 % or less. At drug loads of 75 % or higher, the drug mechanical properties may dominate and also polymer choice when using typical amounts of around 25–30 % w/w increasingly has little impact on modulation of release profiles for highly soluble drugs. One thus faces the challenges of inadequate tablet compaction properties coupled with inadequate control of drug release kinetics. Additionally, the acceptable upper tablet size limit and mass limit for swallowing by a patient and to assure compliance ranges from 800 to 1,400 mg, therefore requiring the amount of added excipients to be minimized [2]. Commercial examples of tablets approaching this limit include metformin 750 mg extended-release tablets (Glucophage XL, Bristol-Myers Squibb), niacin extended release with lovastatin immediate release (Advicor, various strengths, AbbVie), ranolazine 1,000 mg extended-release tablets (Ranexa, Gilead), and metformin/sitagliptin (Janumet XR, Merck).

Approaches to overcome these limitations have included simple crystal and particle coating and preparation of microbeads with insoluble polymers such as ethylcellulose and methacrylic acid copolymer, thus maximizing surface area to volume coverage of the rate controlling excipients. Examples of these approaches include potassium chloride 10 mEq extended-release tablets (Klor-Con, Upsher Smith) and metoprolol succincate 25, 50, 100, and 200 mg extended-release tablets (Toprol XL, AstraZeneca). However, these processes require the use of organic solvents and

fluid bed coating with long cycle times. Alternatively, instead of coating with hydrophobic polymers, excipients such as waxes and magnesium stearate can be incorporated *into* a controlled-release dosage form to provide physical diffusion barriers while minimizing overall excipient volumes [2, 3]. However, such approaches have found limited applications due to lack of robustness at commercial manufacturing scale and variability due to food-dependent in vivo results.

A further approach to overcome these limitations has been the use of matrix tablets combined with additional release controlling film coatings (matrix-reservoir combination systems) [4]. However, such an approach adds cost and manufacturing complexity as compared to simple matrix systems.

In addition the opposite challenge, i.e., the extended delivery of low soluble drugs, is also encountered with increasing frequency. In this case, hydrophilic erodible systems using intermediate molecular weight grades of polymers such as HPMC or hydroxypropyl cellulose, HPC may be well suited; however additional means of solubilization such as inclusion of large amounts of cyclodextrins or surfactants have to be attempted. This again can push the limits of dosage form size.

For both these scenarios where limited or no feasible technical options exist, twin-screw extrusion processing may offer a commercially viable and practical solution. This is further discussed in this chapter.

10.3 Hot-Melt Twin-Screw Extrusion: An Enabling Technology for Controlled Release

10.3.1 General Background

Extrusion can be generally described as a process by which an extrudate with new or composite properties is formed by forcing one or more components through an orifice under controlled conditions of temperature, shear, and pressure [5]. Extrusion is widely applied in many industries and is generally regarded as a mature technology, having been largely developed and refined during the nineteenth and twentieth centuries. However, extrusion remains highly relevant in food and plastics manufacturing and is now a significant emerging technology for solid dosage form manufacturing.

A major advantage of twin-screw extrusion over conventional unit processes such as mixing, powder blending, high shear granulating, and roller compacting is that these unit processes can be combined into essentially a single operation within the extruder. Moreover, the extent of these individual aspects of the overall process can be readily controlled and manipulated by the extruder design. In particular screw configurations and die designs offer large flexibility as does the option of employing various temperature profiles and shear rates. Finally, while extruders are suitable for a batch mode of manufacturing in the case of smaller volume, but high value pharmaceutical products, the process is inherently a continuous one. This also makes it of utility in the manufacturing of large volume products as it allows for a smaller, more efficient footprint with discrete manufacturing unit operations validation

and quality control. Additionally, due to the small footprint and contained nature of the feeding mechanism and the extruder barrel, the process can be readily isolated in the case of highly potent compounds.

10.3.2 Basic Process Description

A basic twin-screw extruder consists of a drive system, a series of independently controlled modular barrel blocks, two screws with an individual screw element arranged on a screw shaft, a die, and connections to utilities and controls. Additional downstream equipment such as conveyor belt, calendering rolls, and pelletizers and mills are common. An illustration of a pilot-scale 18 mm extruder suitable for formulation development and scale-up is shown in Fig. 10.1. The equivalent model in GMP configuration is shown in Fig. 10.2. A schematic layout for a typical extruder is given in Fig. 10.3 and typical screw designs are shown in Figs. 10.4 and 10.5. Several excellent reference texts have been written on pharmaceutical extrusion technology and the reader is referred to these for more detailed process descriptions [6, 7].

Fig. 10.1 Pilot-scale 18 mm Leistritz ZSE extruder as used in some of the work highlighted in this chapter (picture courtesy of Leistritz Extrusionstechnik/Germany)

Fig. 10.2 Leistritz ZSE 18 PH extruder, 18 mm barrel diameter, suitable for GMP manufacturing (picture courtesy of Leistritz Extrusionstechnik/Germany)

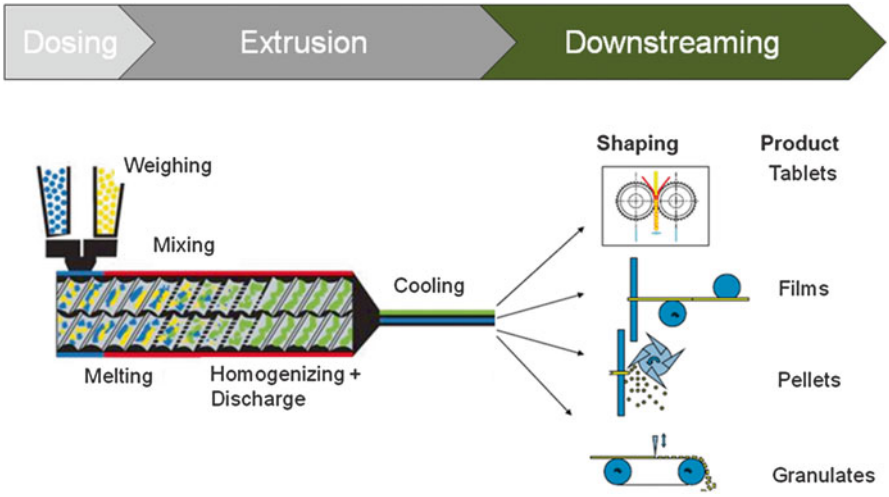

Fig. 10.3 Schematic of the extrusion process

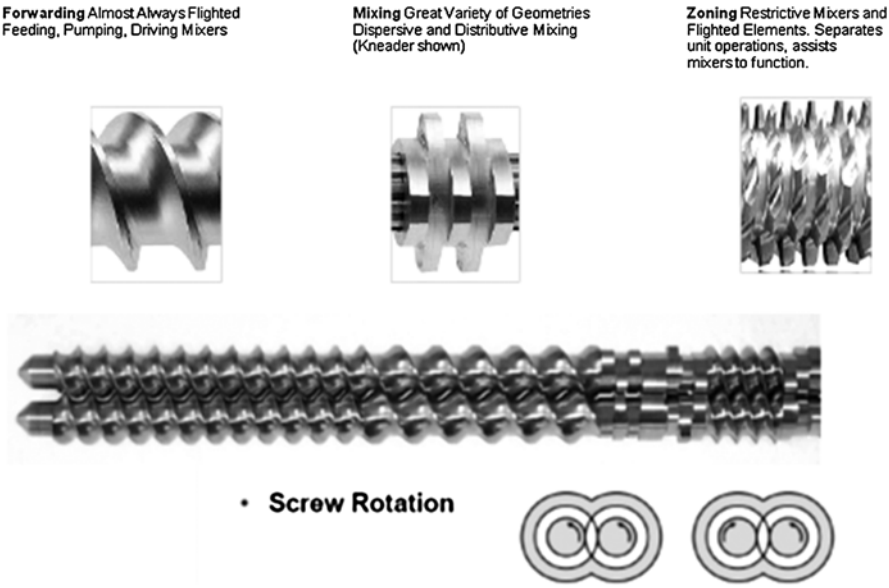

Fig. 10.4 Typical extruder screw element design options (picture courtesy of Leistritz Extrusionstechnik/Germany)

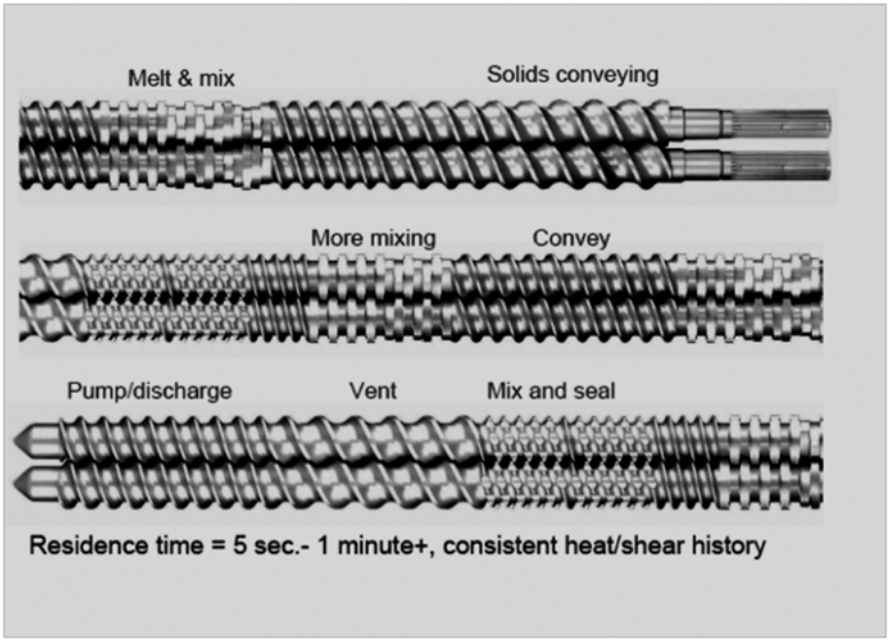

Fig. 10.5 Various co-rotating screw configurations based on different assemblies of elements (picture courtesy of Leistritz Extrusionstechnik/Germany)

10.3.3 Polymers Used for Extrusion

The selection of the polymers for hot-melt extrusion mainly depends on factors such as the thermoplasticity of the polymer, drug–polymer miscibility, polymer stability, and the desired drug release kinetics. Thermoplastic polymers are typically preferred as they can be processed with the extruder at suitable temperatures without affecting the stability of volatile or heat-sensitive drugs. Plasticizers are often added to the polymer if the processing temperature is not suitable for the drug. In some cases, the drug itself can be an effective plasticizer. Polymers used in hot-melt extruded dosage form range from water-soluble ones used to achieve diffusion-dependent drug release kinetics to water-insoluble polymers which can be employed to achieve diffusion- and erosion-dependent drug release mechanisms.

Commonly used, pharmaceutically approved polymers include the cellulose derivatives (hydroxypropylcellulose [HPC], hypromellose [HPMC], ethylcellulose [EC], hypromellose acetate succinate [HPMCAS], cellulose acetate [CA], CA phthalate [CAP]), vinyl polymers (polyvinylpyrrolidones [PVP], copovidone [PVP-VA]), polyethylene oxide (PEO), polyethylene glycol (PEG), and methacrylates (Eudragit™ series) [8]. Hydrophilic polymers such as cellulose ethers (HPC and HPMC) and vinyl lactam polymers (PVP and PVP-VA) are most frequently used as release modifiers and solubilizing carriers. McGinity et al. [9] have also demonstrated the use of natural polymers such as chitosan and xanthan gums as hydrophilic release retardants in hot-melt extrusion applications.

10.3.3.1 Cellulose Derivatives

Cellulose ethers are chemically modified versions of a naturally occurring polysaccharide. Each glucose unit in the polysaccharide, linked to its neighbor by β-1-4 glycoside bonds, has three hydroxyl groups that can be derivatized by alkalization to have hydroxypropyl, hydroxypropyl methyl, and many other semisynthetic cellulosics (Fig. 10.6).

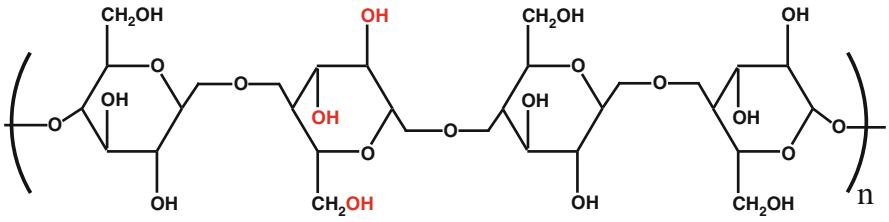

Fig. 10.6 Representative structure of cellulose

Table 10.1 Thermal, physical, and mechanical properties of hydroxypropylcellulose (HPC) (based on manufacturer's data for Klucel™, adapted from data from [8])

Property	HPC	Method
Solid State—particle size (μm)	Mean diameter-50–80 μm for fine grind and 250–300 μm for regular grind	Sympatec Helos laser diffraction
Molecular Weight range (Da)	40,000–80,000	
Glass transition temperature range (°C)	−4.0 to −4.5	DSC: TA instruments DSC Q2000 software
Melting temperature range depending on the molecular weight (°C)	182–191	TA instruments
Melting temperature range (°C)	150–210	
Processing temperature (°C)	100–130	Based on Leistritz ZSE 18HP
Processing temperature (°C) maximum	270–285	DSC: TA instruments DSC Q2000 software
True density (g/cm^3)	1.200–1.214	Mirometrics AccyPyc 1300 Pycnometer
Amorphous density (g/cm^3)	1.088	Instron Capillary Rheometer
Crystalline density (g/cm^3)	2.054	X ray diffraction
Bulk density (g/cm^3)	0.28–0.39	
Crystallinity (%)	14.9	Water-cast film/instron capillary rheometer/X ray diffraction

10.3.4 Hydroxypropylcellulose

The thermal and mechanical properties of hydroxypropylcellulose (available commercially from Ashland Inc. as Klucel™ HPC and Nippon Soda, Nisso™ HPC) (Table 10.1), make it pliable and easy to extrude. HPC has a low glass transition temperature, T_g, of approximately −4.5 °C which provides for a low-melt viscosity and fast-melt flow properties, depending upon the molecular weight of the polymer used (Fig. 10.7). Low molecular weight grades of HPC are often utilized as carriers to attain solid dispersions of poorly soluble drugs [10] and typically do not require plasticizers to melt extrude. The hydroxyl groups of the cellulose backbone and the incorporated substituent hydroxypropoxyl groups are capable of donating hydrogen bonds to active pharmaceutical ingredients (APIs) with hydrogen bond accepting groups. HPC is most capable of stabilizing amorphous dispersions of APIs with hydrogen bond accepting groups. One of the limitations of HPC for use as solid dispersion carrier is its low T_g. This tends to impart a lower T_g to the drug–polymer dispersion which predisposes the dispersion to recrystallization. As a rule of thumb, the T_g of the resultant dispersion should be 50 °C above the highest anticipated storage temperature, e.g., 50–70 °C higher than the accelerated stability temperature of 40 °C. Higher molecular weight grades of HPC (commercially available from Ashland, Klucel HPC HXF and Klucel HPC MXF) are typically recommended for controlled-release applications [11, 12].

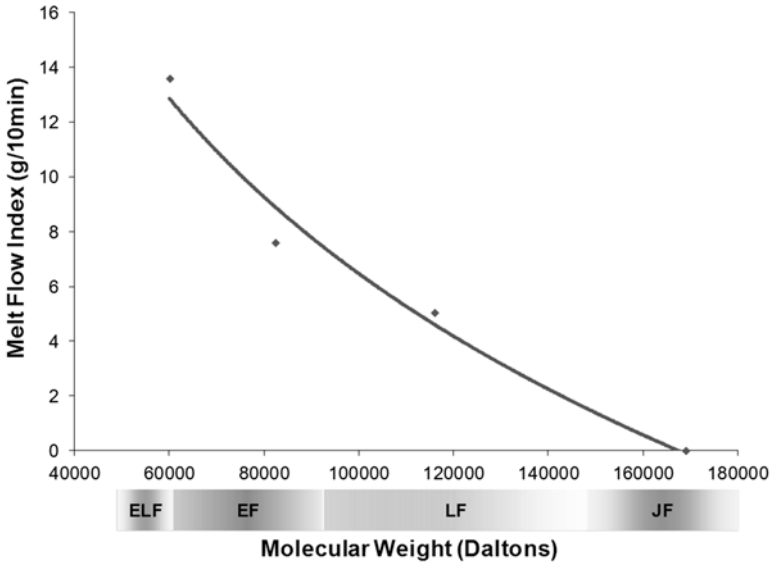

Fig. 10.7 Effect of molecular weight on the melt flow of Klucel™ hydroxypropylcellulsoe (HPC) at 150 °C using ASTM D1238

10.3.4.1 Hypromellose and Hypromellose Acetate Succinate

HPMC is available in several grades that vary in viscosity and extent of substitution (commercially available from Ashland Inc. as Benecel™ HPMC and from Dow Chemical Co. as Methocel™ HPMC grades). The T_g of these polymers varies from 178 to 202 °C depending upon the molecular weight. Due to this high T_g it may therefore require the addition of plasticizers, up to 30 % w/w, to enable melt extrusion. The methoxyl groups are comparably very weak hydrogen bond acceptors, relative to the hydroxypropoxyl groups but, like HPC, HPMC is most able to interact with APIs with hydrogen bond accepting groups. Associated with these hydrogen bonding propensities is recrystallization inhibition which is useful in stabilizing amorphous drugs and thereby enhancing the bioavailability of poorly soluble drugs. The supersaturated levels generated by dissolution of the amorphous solid dispersion can arise from the stabilizing effects of the polymers [13] or the complexation of the crystalline drugs in the polymer matrix, hence reducing the degree of supersaturation and lower thermodynamic tendency toward recrystallization [14]. Higher molecular weight grades of HPMC have been used successfully as release modulators and stabilization enhancers for controlled release of poorly soluble drugs [15].

HPMCAS was originally developed as an enteric polymer for aqueous dispersion coating. The enteric coating prevents drug dissolution in the acidic pH environment of the stomach in order to reduce drug degradation or ameliorate stomach irritation. HPMCAS has a cellulose backbone with hydroxypropoxy, methoxy, acetyl, and

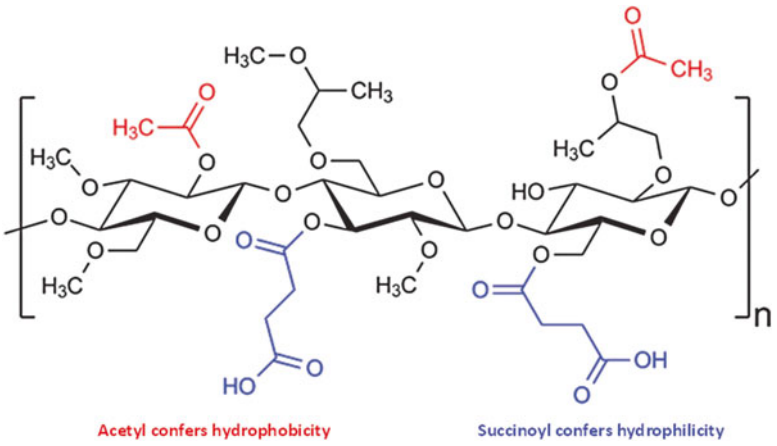

Fig. 10.8 Representative structure of hypromellose acetate succinate (HPMCAS)

succinoyl substituent groups (Fig. 10.8). There are six grades available commercially (AquaSolve™ HPMCAS from Ashland Inc.; Aqoat™ HPMCAS from Shin-Etsu Chemical Co. Ltd) based on the physicochemical properties of the polymer. The F (fine) and G (granular) grades differ only in their particle size, whereas L, M, and H grades are chemically different and vary in their pH solubility. The L, M, and H grades dissolve at pH ≥ 5.5, 6.0, and 6.8, respectively. Thus, the release of the drug in the gastrointestinal tract from a tablet dosage form containing these polymers can be controlled as required by using a suitable grade of the polymer. HPMCAS is an amorphous polymer and has a T_g of about 120–125 °C. The hydroxyl groups of the cellulose backbone and the 2-hydroxypropoxyl substituent groups are capable of donating hydrogen bond to APIs with hydrogen bond accepting groups. The acetyl and succinoyl groups are capable of accepting hydrogen bonds from APIs which is important in stabilizing solid dispersions by inhibiting recrystallization. The overall stabilization effect is attributed to the interaction between API and the polymer functional groups, including specific hydrophobic interactions between the drug and the acetyl groups. Due to the relatively poor thermal plasticity of HPMC and HPMCAS, plasticizers or co-formulation with another more thermoplastic polymer as an extrusion aid may be necessary for melt extrusion of HPMC and HPMCAS.

10.3.4.2 Polyethylene Oxide

Polyethylene oxides (PEOs) are nonionic homopolymers of ethylene oxide represented by the formula $(OCH_2CH_2)_n$. These high molecular weight hydrophilic polymers are available as white, free-flowing powders and are manufactured by Dow Chemical Company under the trade name of POLYOX™. The pharmaceutical grades of POLYOX are available in molecular weight ranges of 100,000–7,000,000 Da

Table 10.2 Commercial grades of polyethylene oxide used in the pharmaceutical industry (based on manufacturer's data for POLYOX™)

POLYOX resins	Molecular weight (Da)	Aqueous viscosity range at 25 °C (m Pa s)
WSR N-10 NF	100,000	12–50 (at 5 % w/v)
WSR N-80 NF	200,000	65–115 (at 5 % w/v)
WSR N-750 NF	300,000	600–1000 (at 5 % w/v)
WSR 205 NF	600,000	4,500–8,800 (at 5 % w/v)
WSR 1105 NF	900,000	8,800–17,600 (at 5 % w/v)
WSR N-12 K NF	1,000,000	400–800 (at 2 % w/v)
WSR N-60 K NF	2,000,000	2,000–4,000 (at 2 % w/v)
WSR 301 NF	4,000,000	1,650–5,500 (at 1 % w/v)
WSR coagulant NF	5,000,000	5,500–7,500 (at 1 % w/v)
WSR 303 NF	7,000,000	7,500–10,000 (at 1 % w/v)

(Table 10.2). Despite its high molecular weight, POLYOX is highly crystalline and has a melting point around 65 °C, above which the polymer becomes thermoplastic. Due to its low melting point and good melt flow index it's considered as a suitable polymer for use in hot-melt extruded formulations. The high molecular weight grades require plasticizer addition in order to enable melt extrusion at moderate temperatures [16]. Zhang and McGinity [17] described a novel method to prepare POLYOX sustained-release matrix tablets using a single screw extruder employing chlorpheniramine maleate as a model drug. The influence of PEO properties on drug release was investigated. PEG 3350 was included as the plasticizer to assist the extrusion processing and 4.5 mm diameter rods were extruded and cut across the diameter of the rod to yield tablets. The stability of PEO was studied as a function of polymer type, temperature, and residence time in the extruder. They demonstrated that excellent mixing of the components occurred in the barrel of the extruder, since the content uniformity of the extruded tablets was within 99.0–101.0 %. An increase in the amount of plasticizer was found to increase the drug release, whereas increasing drug concentration in the matrix only slightly affected drug release up to drug loading levels around 20 % w/w. Combinations of different grades of POLYOX with other polymers may enable formulators to tailor release profiles of the drugs as well as enhance the melt-extrusion processing.

10.3.5 Polyvinyl Lactam Polymers

Polyvinyl lactam polymers available as homopolymers, such as polyvinylpyrrolidone (povidone, commercially available from Ashland Inc. as Plasdone™ and BASF SE as Kollidon™ grades), or as copolymers, polyvinylpyrrolidone-vinyl acetates (copovidones, commercially available from Ashland Inc. as Plasdone™ and BASF SE as Kollidon™), have been widely used in the pharmaceutical industry

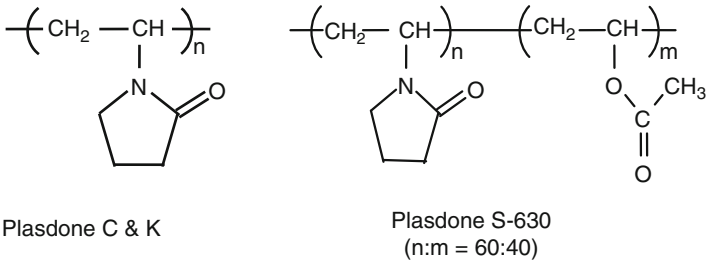

Fig. 10.9 Representative structure of povidone (Plasdone C and K) and copovidone (Plasdone S-630)

for more than 40 years (Fig. 10.9). These polymers are synthesized by radical polymerization of the corresponding monomers and depending upon the reaction conditions different polymer properties can be obtained.

Povidones (Plasdone™ *K* grades) are commonly used as solubilization carriers. The T_g ranges from 120 to 174 °C depending upon the *K* value. They are compatible with most plasticizers and may require the addition of plasticizers for melt extrusion. The monomer units are capable of accepting hydrogen bonds. Copovidone PVP-VA copolymers (Plasdone™ S630) have a T_g around 106 °C that makes it ideal for melt-extrusion applications. It is both aqueous and organosoluble and both monomer units are capable of accepting hydrogen bonds. Its limitation in HME application is its hygroscopicity. Both povidones and copovidones are water soluble which limits its applicability in controlled-release applications. They are most frequently used to enhance solubility of poorly soluble drugs [18] and in combination with cellulose ethers in controlled-release applications [15].

Graft copolymers can also be obtained by grafting monomers onto other polymers. These polymers differ significantly in their hydrophilicity/lipophilicity properties which are derived from the graft components and grafted side chains. One such graft polymer, Soluplus®, was developed by BASF in 2009. It was produced by grafting vinylcaprolactam and vinyl acetate onto polyethylene glycol in a copolymerization reaction. As a result, it has a backbone of polyethylene glycol and side chains comprising the two vinyl monomers. This gives the product an amphiphilic character and it is mostly utilized for solubility enhancement. It has a low T_g and dense particle structure that enables melt extrusion to be carried out at extremely high-throughput rates as the polymer can be fed into the extruder rapidly [18].

BASF's Kollidon® SR, which is a formulated mixture of the two polymers polyvinyl acetate and povidone in the ratio of 8:2, is designed to be used in sustained-release applications. The insoluble polyvinyl acetate provides for an extremely high degree of plasticity and also presents a diffusion barrier that slows down the release of the drug. The water-soluble povidone creates micropores in the framework of the polyvinyl acetate through which water can penetrate the entire system, thereby dissolving the active drug and allowing the diffusion of the drug. Özgüney et al. [19] recently demonstrated the utility of Kollidon SR in melt-extrusion applications.

10.3.6 Use of Twin-Screw Extrusion in Controlled-Release Matrix Applications

10.3.6.1 Recent Advances for Controlled Release of Highly Soluble Drugs

The limitations of conventionally manufactured hydrophilic matrix high doses of highly soluble drugs have been described in Sect. 10.2. Hot-melt extrusion offers an elegant means to overcome many of these limitations.

Recently melt extrusion has been utilized for various controlled-release applications in which extrudates are milled to produce granules and compressed into final tablet dosage forms. These formulations are not necessarily based on water-soluble polymers alone but may also require water-insoluble polymers in order to optimize release profiles and modulate release of extremely highly soluble drugs. In 2010, Pinto and coworkers [20, 21] investigated the feasibility of using hot-melt extrusion as an alternative to wet granulation or direct compression for the preparation of highly soluble drugs at high loads (75 % w/w drug load). Higher molecular weight grades of HPC, Klucel™ HF hydroxypropylcellylose and Aqualon™ ethylcellulose, were used as hydrophilic and hydrophobic controlled-release polymer, respectively, using metformin as a model high-dose, high solubility drug. The metformin tablets made by employing hot-melt extrusion were twice as strong and also smaller and consequently less porous when compared to the analogous tablets made by wet granulation or direct compression (Table 10.3, Fig. 10.10). The improved mechanical properties and smaller tablet size for the same weight of unit dose can be attributed to the intimate mixing of drug with polymer in the molten state and the substantial elimination of air in the extrudate. In addition, the extrusion process also resulted in improved compactibility and reduced elastic recovery as evidenced by the enhanced tablet strength and reduced friability. The reduced porosity of the metformin tablets prepared using hot-melt extrusion resulted in a dramatic improvement in the release retardation of metformin as compared to wet granulated and direct compression tablets (Fig. 10.11). These differences can be attributed to the lower porosity of the hot-melt extruded tablets which resulted in slower ingress of media into the tablet (Fig. 10.12) and slower diffusion of dissolved drug out of the tablet, notably in the early time phase (first 30 min). After this initial period a sufficiently strong gel layer envelops the tablet to control the further ingress of water into the system. Higher

Table 10.3 Physical characteristics of extended-release tablets prepared using different manufacturing processes

Unit process	Granule density (g/ml)	Tablet volume (ml)	Porosity (%)	Tablet strength (kp) 3 kN pre-compression 15 kN main compression
Extrusion	1.30	0.8	3.4	14.2
Wet granulation	1.35	0.9	12.7	4.0
Direct compression	1.35	0.9	15.3	5.0

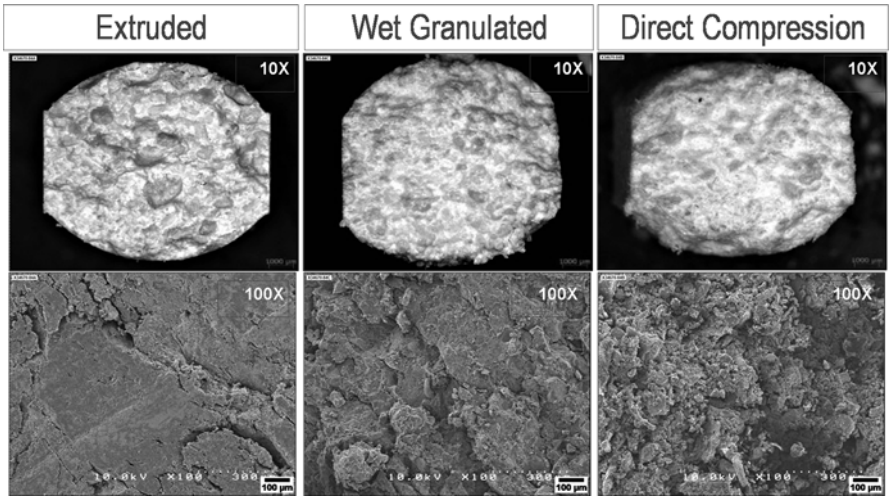

Fig. 10.10 Porosity of metformin hydrochloride tablets prepared by different processes. Scanning electron microscopy pictures of the cross section of the tablets indicates that tablets made by the extrusion process were denser and less porous relative to tablets made by the alternate processes

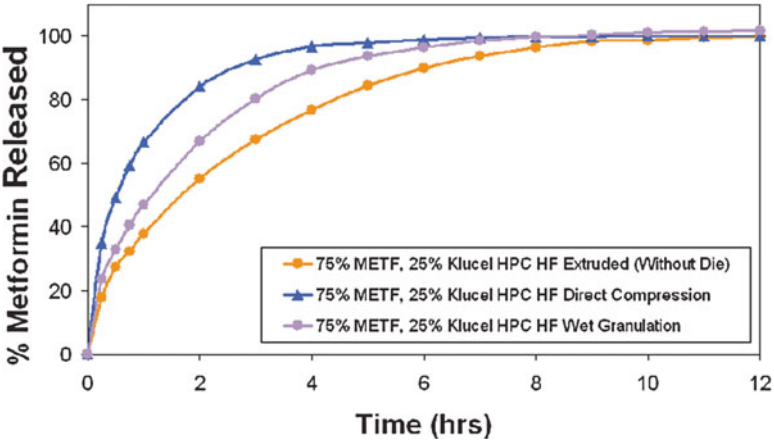

Fig. 10.11 Dissolution profiles of metformin tablets. Tablets made by the extrusion process exhibited a reduced rate of drug release relative to tablets made by other processes (USP apparatus 1; 6.8 phosphate buffer; 100 rpm)

MW hydroxypropylcellulose grades formed stronger gel layers as evidenced by the slower tablet erosion rates and slower drug release profiles.

Successful application of hot-melt extrusion for modified-release dosage form was also reported by Serajuddin et al. [22]. They were also able to develop controlled-release formulations using the higher molecular weight grade of Klucel™ HPC HF. Additionally, they were able to demonstrate the in vivo performance of the formulation in a clinical study, where the matrix tablet demonstrated a plasma t_{max}

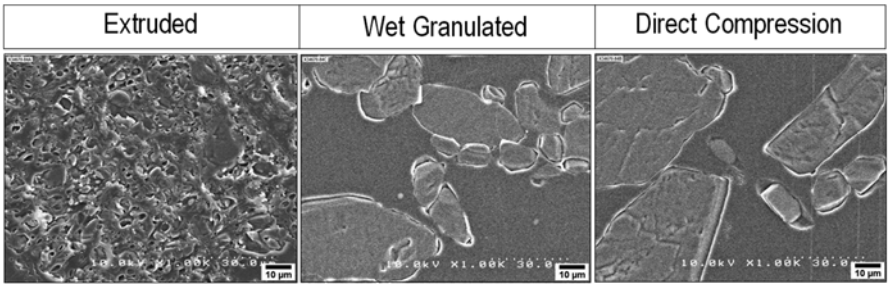

Fig. 10.12 Porosity of metformin hydrochloride extruded granules. Scanning electron microscopy pictures of the cross section of granules embedded in epoxy resin indicate that granules made by the extrusion process had more internal voids relative to granules made by alternate processes. This may explain the lower granule density for those made by extrusion relative to those made by alternate process

of 4–8 h, thus providing proof of concept for hot-melt extrusion processing as an enabling controlled-release technology. Using this technology a high-dose, highly soluble drug was delivered in a smaller tablet than what could be manufactured by conventional granulation techniques.

In 2000, Zhang and McGinity [23] conducted a study to investigate the properties of polyvinyl acetate (PVA) as a retardant polymer and to study the drug release mechanism of theophylline from matrix tablets prepared by hot-melt extrusion. They found the release rate of the drug to be dependent on the granule size, drug particle size, and drug loading in the tablets. As the size of hot-melt extruded theophyllline/PVAc granules was increased, there was a significant decrease in the release rate of the drug. Higher drug loading in the hot-melt granules also showed higher release rates of drug. Water-soluble materials such as PEG 400 and lactose were demonstrated to be efficient release rate modifiers for this system.

Fukuda et al. [9] prepared tablets utilizing a hot-melt extrusion process containing chlopheniramine, chitosan, and xanthan gum. Drug release from tablets containing either chitosan or xanthan gum was dependent on media pH and buffer species and the release mechanisms were controlled by the solubility and ionic properties of the polymers. Tablets which contained both chitosan and xanthan gum exhibited extended release which was pH and buffer species independent. In 0.1 N HCl, the dual polymer tablets formed a gel layer that retarded drug release even after switching to pH 6.8 and 7.4 phosphate buffers, and when media contained high ionic strength. As the tablets without chitosan did not form a gel-like structure in 0.1 N HCL, loss of drug release retardation was seen on switching media pH for these single polymer tablets.

From the research described in this section, it can be seen that hot-melt extrusion provides a robust manufacturing process to provide for tablets with higher compactibility and lower friability compared with equivalent formulations made by conventional processes. The process can result in tablets of reduced size for high-dose drugs and combination products, relative to conventional approaches by decreasing the need for relatively large amounts of excipients.

10.4 Recent Advances for Controlled Release of Low Soluble Drugs

Increasingly drug candidates emerging from discovery programs suffer from poor water solubility. This can lead to a variety of problems such as rate-limiting dissolution, slow absorption, and limited bioavailability [24]. Extended release of poorly water-soluble drugs is one of the most challenging issues for the formulators. Solid dispersion formulation is a commonly used approach to improve bioavailability by enhancing drug solubility. The solid dispersion approach usually produces immediate-release forms. The combined and synergistic approaches of solid dispersion and extended release for dosage forms containing poorly water-soluble drugs have become a valuable technique for achieving optimal drug bioavailability in a controlled manner and thereby providing the predictability and reproducibility of the drug release kinetics.

In recent years, significant work has been done in the application of hot-melt extrusion process for the preparation of solid dispersions [25, 26]. The utility of hot-melt extrusion for the controlled release of drugs has been discussed in the previous section. Ozawa et al. [27], Nakamichi [28], Miyagawa [29], and Sato [30] developed the twin-screw extruder method for the preparation of solid dispersions of water-insoluble and soluble drugs by controlling both kneading and heating at the same time under the fusion point of each drug as well as feed rate, screw speed, and barrel temperature. Their results showed they could achieve increased solubility of poorly soluble drugs and decreased solubility of water-soluble drugs.

Lian et al. [31] investigated the feasibility of combining hot-melt extrusion with thermoplastic water-soluble polymers, a technique to simultaneously enhance the solubility of poorly soluble compounds and to facilitate the production of nifedipine extended-release hydrophilic mini tablets that deliver the drug payload over a period of 8 h. A 75 mg dose (representing 20 % drug load) was selected to achieve a fivefold supersaturation concentration in FaSSIF (fasted simulated intestinal fluid). Table 10.4 and Fig. 10.13 show the process conditions and twin-screw extruder setup for a blend consisting of 20 % nifedipine, 40 % Benecel™ HPMC K15M, and 40 % copovidone Plasdone™ S-630. They found that several formulation variables such as drug loading (Fig. 10.14), level and ratio of HPMC and copovidone (Fig. 10.15), molecular weight of HPMC (Fig. 10.16), and processing variables such as pelletizer feed speed and die orifice diameter had profound impact on degree and sustainment of supersaturation achieved and drug release rate.

Pure copovidone without HPMC did not show sufficient release retardation. When a 1:1 ratio of copovidone and HPMC (750 cps instead of 15,000 cps) is used, extended release over 4 h was produced and a fourfold supersaturation concentration equivalent to 60 mg was achieved.

HPMC is a known recrystallization inhibitor [10, 32] and higher molecular weight polymer grades inhibit the molecular mobility of the drug in a solid dispersion. Therefore, the higher molecular weight HPMC might not only slow drug release but also maintain higher degree of supersaturation. Effect of molecular

Table 10.4 Typical process conditions for the preparation of nifedipine extended-release mini tablets by extrusion

Extruder process temperature								Extruder process condition				Pelletizer process condition	
Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8	Feeder speed (RPM)	Extruder speeder (RPM)	% Load	Melt pressure (PSI)	Feedroll speed (RPM)	Cutter speed (RPM)
50 °C	100 °C	120 °C	140 °C	140 °C	140 °C	140 °C	137 °C	100	100	30	350	55	65

Fig. 10.13 Extruder and pelletizer setup for nifedipine mini tablet extrusion

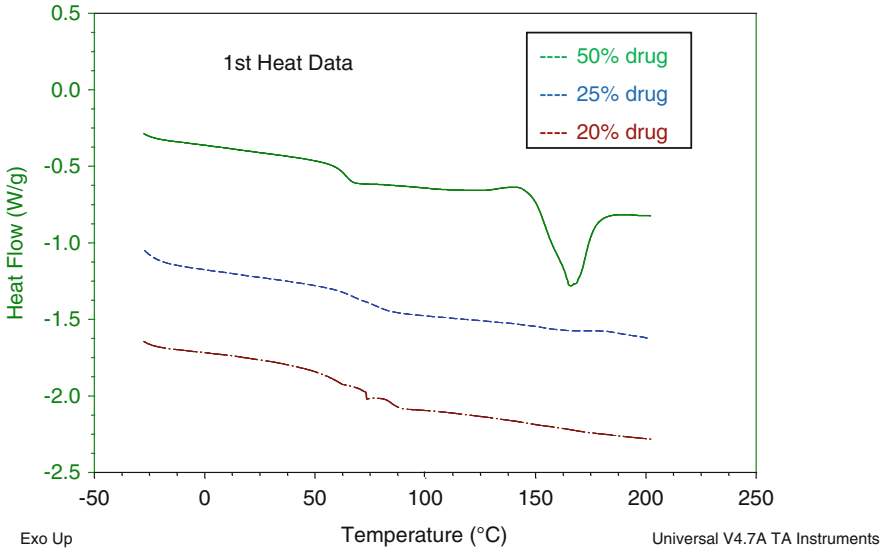

Fig. 10.14 DSC thermograms illustrating the effect of nifedipine loading. Amorphous dispersions could be obtained at 20 and 25 % w/w drug loading but not at 50 % w/w drug loading as evidenced by the melting endotherm for nifedipine at 170–180 °C

weight of HPMC on drug release and supersaturation is shown in Fig. 10.16. Combining HPMC and copovidone in the formulations (40 % Benecel™ K15M HPMC, 40 % Plasdone™ S-630 copovidone, 20 % drug) maintained supersaturation at 0.70 mg/ml for up to 8 h in contrast to the formulation where 750 cps HPMC was used and with extended release of only 4 h. In addition, release profiles reaching 100 % drug released in 8 h could be achieved under non-sink conditions.

The effect of surface area/volume ratio (SA/V) of the hydrophilic matrix mini tablets was studied by varying the die orifice diameter and pelletizer feed speed.

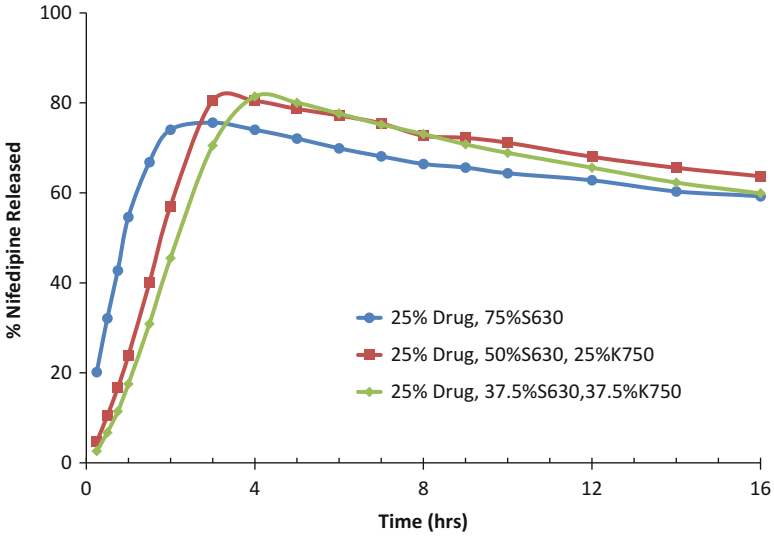

Fig. 10.15 Effect of HPMC (750 cps grade) to copovidone ratio on the release of nifedipine from mini tablets made by extrusion

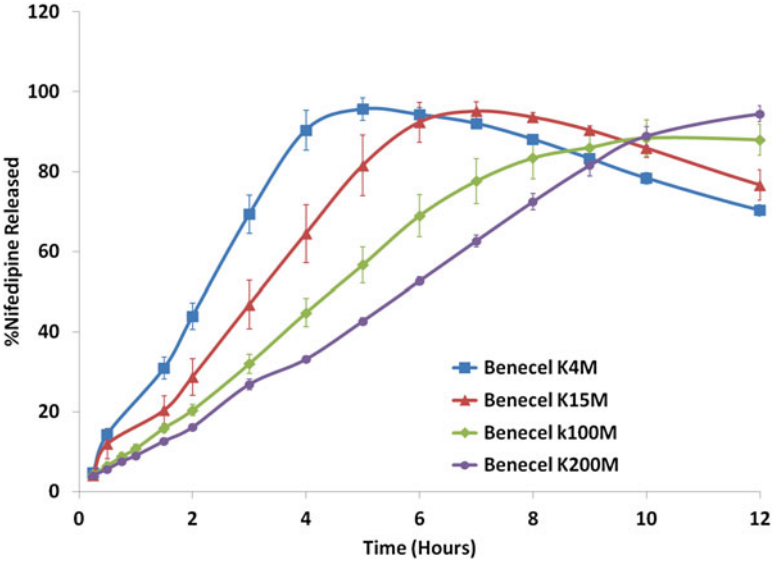

Fig. 10.16 Effect of HPMC molecular weight on release of nifedipine from mini tablets made by extrusion (tablets were 25 % w/w nifedipine, 37.5 % w/w/copovidone, and 37.5 % w/w HPMC of varying molecular weight)

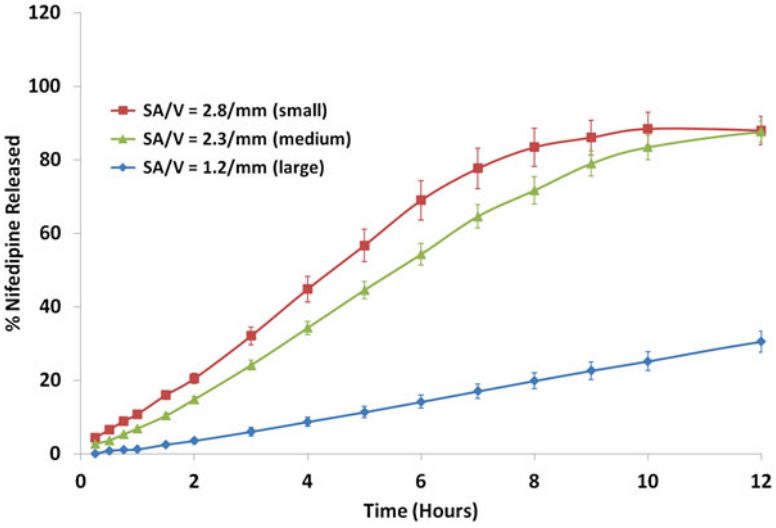

Fig. 10.17 Effect of tablet size expressed as surface area-to-volume ratio (SA/V) on release of nifedipine from mini tablets made by extrusion. Tablet size is inversely proportional to SA/V

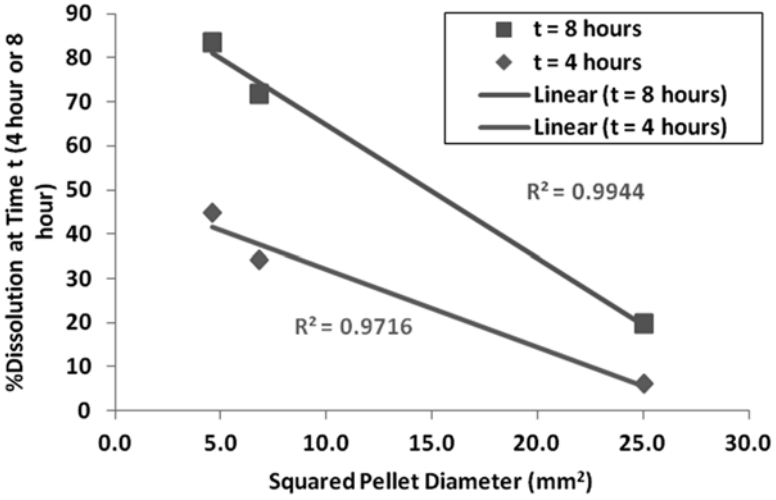

Fig. 10.18 Relationship between mini tablet surface area and drug release

The larger mini tablets have a significantly slower drug release as illustrated in Fig. 10.17. It should be noted that tablet size is inversely proportional to SA/V; thus the larger the SA/V, the smaller the tablet size. Conversely the release rate was found to be directly proportional to mini tablet surface area (Fig. 10.18). Hot-melt extrusion processing facilitated the formation of a solid solution with a continuous

hydrophilic matrix structure that was shown to control the drug diffusivity; simultaneously the extruded strand was conveniently cut into mini tablets without the need for further processing and tablet compaction.

10.5 Conclusion

Over the last 40 years hydrophilic matrix systems have emerged as a major technology platform for the oral controlled delivery of drugs. Major advances have been made in the understanding of drug release mechanisms, in modeling of drug delivery systems, and in the rational design and manufacturing of controlled-release matrix systems and polymers for hydrophilic matrix dosage forms.

Twin-screw extrusion represents an enabling technology and step change to further enhance the value of hydrophilic matrix systems. Specifically as highlighted in this chapter, hot-melt extrusion enables the design of formulations and delivery of highly soluble as well as insoluble drugs and in a manner not possible with traditional manufacturing unit processes. In addition, twin-screw extrusion represents an opportunity to replace traditional batch unit processes such as fluid bed, high shear granulations, and batch blending with a more robust and economical continuous manufacturing process. Added advantages which accrue involve the ease of scale-up from pilot to manufacturing scale. In this regard, work is ongoing on the development of continuous manufacturing systems involving extrusion as a key enabler not only in hot-melt modes but also as a means of more efficient wet granulation process. An example of this is GEA's new Consigma, continuous manufacturing concept [33]. We therefore expect that the industry will continue to embrace twin-screw extrusion processing and related technologies as a source of innovation in controlled release as well as other applications.

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