Pharm Res (2011) 28:2353–2378
DOI 10.1007/s11095-011-0449-y

EXPERT REVIEW

Controlled Release Systems Containing Solid Dispersions: Strategies and Mechanisms

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Received: 5 January 2011 / Accepted: 7 April 2011 / Published online: 7 May 2011

ABSTRACT In addition to a number of highly soluble drugs, most new chemical entities under development are poorly water-soluble drugs generally characterized by an insufficient dissolution rate and a small absorption window, leading to the low bioavailability. Controlled-release (CR) formulations have several potential advantages over conventional dosage forms, such as providing a uniform and prolonged therapeutic effect to improve patient compliance, reducing the frequency of dosing, minimizing the number of side effects, and reducing the strength of the required dose while increasing the effectiveness of the drug. Solid dispersions (SD) can be used to enhance the dissolution rate of poorly water-soluble drugs and to sustain the drug release by choosing an appropriate carrier. Thus, a CR-SD comprises both functions of SD and CR for poorly water-soluble drugs. Such CR dosage forms containing SD provide an immediately available dose for an immediate action followed by a gradual and continuous release of subsequent doses to maintain the plasma concentration of poorly water-soluble drugs over an extended period of time. This review aims to summarize all currently known aspects of controlled release systems containing solid dispersions, focusing on the preparation methods, mechanisms of action and characterization of physico-chemical properties of the system.

KEY WORDS controlled release solid dispersion · poorly water-soluble drugs · manufacturing methods · physicochemical characterization · rate-controlling mechanism

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ABBREVIATIONS

AAS	atomic absorption spectroscopy
AES	atomic emission spectroscopy
CLSM	confocal laser scanning microscopy
CR	controlled release
CR-SD	controlled-release solid dispersion
DSC	differential scanning calorimetry
EC	ethylcellulose
EPRI	electron paramagnetic resonance imaging
FTIR	fourier transformed infrared spectroscopy
HPMC	hydroxypropyl methylcellulose
HEC	hydroxyethyl cellulose
HPC	hydroxypropyl cellulose
ICP spectrometry	inductively coupled plasma spectrometry
IR-SD	immediate-release solid dispersion
MRI	magnetic resonance imaging
NIR imaging	near infrared imaging
NMR	nuclear magnetic resonance
NSESD	non-self-emulsifying solid dispersion
PCS	photon correlation spectroscopy
PEG	polyethylene glycol
PEO	polyethylene oxide
PVP	polyvinyl pyrrolidone
pH_M	microenvironmental pH
PXRD	powder X-ray diffraction
SD	solid dispersion
SEM	scanning electron microscopy
SESD	self-emulsifying solid dispersion
TEM	transmission electron microscopy
T_g	glass transition temperature
TMDSC	temperature modulated differential scanning calorimetry

INTRODUCTION

Despite several advantages of oral dosage forms, such as the simplicity of administering the drugs, patient compliance, dosage accuracy and flexibility of production, immediate-release solid oral dosage forms usually face challenges in the development of optimized drug delivery systems due to the lack of modulation of gastrointestinal transit time with the minimization of first-pass elimination. In contrast, controlled release (CR) systems have gained much attention in recent years and have become an increasingly important strategy in therapeutic treatment because they allow the pharmacological effect to be maintained by releasing a drug to the desired target site at a controlled rate for an appropriate extended time. CR systems offer several advantages, such as reducing high total dose, reducing dosing frequency and gastrointestinal side effects, and improving patient acceptance and compliance (1). Nevertheless, in oral CR systems, it is difficult to quickly stop the pharmacological action of the drug when poisoning, serious adverse effect, or unwanted intolerance occurs. Some concerns about CR systems also include the reproducibility of pharmacological action being affected by the rate of gastric emptying, different release rates being affected by the integrity and size of the pharmaceutical dosage form and, in general, stability problems (2). Pharmaceutical techniques for controlling the release of drugs, therefore, are the most basic and important factors for these CR drug delivery systems.

However, a number of recent drug candidates have had poor water solubility, which is associated with a variety of inadequate properties, including rate-limiting dissolution, slow absorption and low bioavailability. Although numerous CR oral dosage forms, such as membrane-controlled systems and matrices with water-soluble/insoluble polymers or waxes, have been developed, research on suitable CR systems has recently focused on poorly water-soluble drugs (3). For such CR delivery systems containing a poorly water-soluble drug, the low solubility of drugs is the most important issue to be addressed. Although improving bioavailability by enhancing drug solubility is achievable by altering a drug's structural crystallinity, the simple use of SD alone has had only limited success. The SD generally tends to be immediate-release forms with the inherent drawbacks of high peak drug concentrations in the blood, short times following administration when drug concentrations in the blood reach their t_{max} and relatively short durations of effective concentration levels in the blood (4). To overcome these problems, a combination of SD and CR techniques has become an attractive approach (5) because the supersaturation of drugs can be achieved by applying SDs. The SD technique can be used to enhance the dissolution rate, solubility and oral absorption of poorly water-soluble drugs as well as to sustain the drug release by choosing appropriate CR polymers (6–10). CR-SDs are expected to satisfy the need to improve the dissolution and bioavailability of poorly water-soluble drugs in a CR manner. However, several pharmaceutical aspects, such as complicated processing, low reproducibility of physicochemical properties, formulation development and scale-up, and physical instability, make it difficult to apply SD systems to CR dosage forms. To maintain a supersaturation level of drug for an extended time without recrystallization during its release from the dosage form is an important task because the supersaturation level is decreased when such a diffusion-controlled system remains in contact with water for a long period. Drug recrystallization may occur in varying degrees across the gradient of drug concentration created by water penetration process (5). For this reason, only a few reports on the application of SDs to CR systems have been presented. Many conventional SD approaches are not successful in improving the solubility and dissolution rate of poorly water-soluble drugs, especially weakly acidic or basic drugs.

A specific formula of CR-SD and/or a manufacturing method may be required for each drug, depending on the physicochemical nature of the drug. The drug dissolution behaviors from CR-SDs, therefore, are modulated by both the SD and CR characteristics. Usually, a direct modification of the SD characteristics using water-insoluble or slowly dissolving carriers instead of conventional hydrophilic polymers or a membrane-controlled tablet containing SD have been used in the development of these CR-SDs (11–13). CR-SDs containing pH modifiers could also provide a pharmaceutical strategy for the enhanced but controlled solubility and bioavailability of poorly water-soluble drugs via the maintenance of a pH microenvironment in a solution (14).

In determining the SD characteristics, it is important to note that the dissolution of the active ingredient is influenced by the presence of other components in the formulation, including the carrier, which can be the CR material itself. However, depending on the CR characteristics of the material, which can be primarily insoluble skeleton matrices, hydrophobic and potentially erodible polymers, or hydrophilic polymers, there are usually three primary mechanisms by which the drug can be released from the system: diffusion, erosion, and swelling followed by diffusion.

This review discusses the pharmaceutical strategies and dissolution-modulating mechanisms of the CR-SD systems, a combination of SD and CR techniques containing various types of poorly water-soluble drugs. For these goals, polymers that are widely used as CR carriers and SD techniques are introduced, and then the preparation methods and the physicochemical properties of CR-SD systems are described in detail.

ENHANCED DISSOLUTION AND MECHANISMS OF SOLID DISPERSIONS CONTAINING POORLY WATER-SOLUBLE DRUGS

SDs are usually categorized by their physical states, such as amorphous form, crystalline form, or the intermediate state between these two forms (partially crystalline or amorphous form). They are also categorized on the basis of their molecular arrangement, including eutectics, amorphous precipitations in crystalline matrix solid solutions, glass suspension, and glass solution (15). Finally, SDs can be categorized into different generations of innovation, a classification that actually combines the above characteristics: the eutectics and SDs prepared using crystalline carriers are referred to as first-generation SDs, those with amorphous carriers instead of crystalline are referred to as second-generation SDs, and those with surface-active carriers are referred to as the current generation (16). Because there is already an abundance of reviews of SDs with such various ways of classification, this paper summarizes the SDs into two categories, non-self-emulsifying SDs (NSESDs) and self-emulsifying SDs (SESDs) with brief introduction, and discusses their mechanisms of enhancing drug dissolution as well as the limitations of SDs and resolutions to overcome these.

Non-Self-Emulsifying SDs (NSESDs)

NSESDs refer to SDs composed of carriers or other agents that have no self-emulsifying properties. Hydrophilic carriers are more favorable in these systems, for example, polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), HPMC, cyclodextrins, urea and mannitol (6–10). These carriers are crystalline or amorphous, but the amorphous form is usually preferable because the drug has a better chance to be molecularly dispersed within the amorphous carrier, creating the amorphous SDs for the maximized solubilization of drugs. In contrast, when the drug remains in the crystalline state within the crystalline carriers, the drug in the SDs is not satisfactorily soluble in the carrier, but the drug release rate is still increased—in this case, because of the partial amorphousness of drugs. The enhancement of drug release and bioavailability from these SDs is also attributed to the reduced particle size and the better wettability of the drug rather than to structural changes in drug crystallinity. Additionally, the rapid release of drug can be attributed to the rapid dissolution of the carrier (17). The preparation method for NSESDs can be either the solvent method or the melting method, depending on the physicochemical properties of the drug and carrier.

Self-Emulsifying SDs (SESDs)

In contrast to NSESDs, the carriers in SESDs systems have surface activity or self-emulsifying properties. In the SESD preparation, the carriers are usually melted at elevated temperatures, and the drugs are then dissolved in the molten carriers. These surface-active agents, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions, adsorb drugs onto the surfaces or interfaces of a system, thereby altering the surface or interfacial free energy to reduce the surface and the interfacial tension, through which the dissolution of drug can be increased by preventing the formation of any water-insoluble surface layer. The high surface area of the dissolved vehicle would further facilitate the dissolution of the drug via the finely divided state of the emulsion droplets. Surface-active agents including Gelucire®, Pluronic®, Compritol®, Labrasol®, Transcutol® and tocopheryl polyethylene glycol 1000 succinate (18–20) are carriers commonly used in the preparation of SESDs. Furthermore, these carriers, depending on the type of dosage forms, can improve the solubility or stability of the drug in the liquid preparation, stabilize and modify the texture of semisolid preparations, or alter the flow properties of the final tablet dosage form (21). Compared to the NSESDs, in which the dispersed drug may be more prone to dissociation from the water-soluble matrix, the physical state of drug in SESDs can be improved as long as a continuous drug surface layer is largely maintained by the molecular dispersion of drug in the carrier to form a solid solution. The SESDs are usually filled into hard capsules as hot-melts, which then solidify at cool or room temperature, or are mixed with adsorbents and other free-flowing excipients for subsequent tablet compression.

Limitations of SDs and Overcoming Approaches

In addition to some limitations related to preparation methods such as manufacturing and time cost, scale-up of manufacturing process, etc., physical stability is the most concerning problem of SDs. The amorphous form of the SDs is preferable to increase drug solubility. Unfortunately, this amorphous state is less stable than the crystalline state, resulting in the recrystallization of drug from SDs in the manufacturing process and under storage conditions (16). In the manufacturing process, the subsequent drug crystallization from SD may occur if the drug is dissolved to excessive solubility in a carrier. In storage conditions prone to moisture, which are usually at high risk of inducing intensive drug mobility, the fact that the amorphous state always tends to move to the higher energy level of the crystalline state is one factor leading to recrystallization. The solubility and miscibility of drug in the polymer are

directly related to the stabilization of an amorphous drug against crystallization (22). Below T_g (glass transition temperature), which represents a kinetic boundary of molecular mobility, the stability of the SDs strongly relies on the kinetics of phase separation and/or crystallization instead of thermodynamics. It has been proposed that at the temperature 50°C lower than T_g, the molecular mobility can be neglected and the amorphous solids are stable enough over a period of years (23). Therefore, Qian *et al.* (22) described some challenges in the development of SDs for further investigations of the destabilization mechanism of amorphous SDs as follows: (a) T_g of the system and the best estimation of the drug solubility in polymer across the relevant temperature range are obtained; (b) the drug loading in SD is below the solubility at T_g as long as the dose requirement can be satisfied; (c) in cases of high-dose requirement, the best estimation of drug miscibility in a polymer and miscibility at T_g as the upper limit of drug loading are considered; (d) the hygroscopicity of the SD is evaluated; (e) an appropriate polymer is selected; (f) SDs are manufactured and stored within thermodynamically or kinetically stable temperature whenever possible; and (g) the crystallization kinetics of the drug and the mixture should be studied.

Although SESDs are superior in stabilizing drugs and avoiding drug recrystallization to achieve the highest bioavailability compared to NSESDs, a limitation of both SESDs and NSESDs is the inability to enhance drug dissolution if adequate solubility in a carrier cannot be obtained. Therefore, a conventional SD, which is commonly a binary system of two components, drug and carrier, is not usually successful in enhancing drug solubility or dissolution. For this reason, various pharmaceutical excipients such as solubilizers, surfactants, oils and fatty acids, alone or in the form of mixtures, can be added to the SDs to further improve drug solubility and dissolution rate (24–31). Most solubilizing agents have surfactant properties (e.g., poloxamer, sodium lauryl sulfate, and Tween 80). Importantly, the incorporation of pH modifiers into these systems may be the promising way to enhance drug dissolution because most poorly water-soluble drugs are weakly acidic or basic compounds with pH-dependent solubility (32–35). The microenvironmental pH (pH_M), which has been defined as the pH of the saturated solution in the immediate vicinity of the drug particles, is created by pH modifiers included in these systems and therefore modifies the drug release rate (35). An acidifier or alkalizer is commonly used to enhance the dissolution rate of weakly basic drug or weakly acidic drug by decreasing or increasing the pH_M of the dosage forms, respectively. However, not all weakly basic drugs or weakly acidic drugs follow this principle. For example, the dissolution of telmisartan, which is poorly soluble in intestinal fluid, can be substantially enhanced by adding alkalizers (32). Therefore, the optimal choice should be decided for each specific drug after a preliminary investigation of its solubility. pH modifiers are usually added to the SD preparation together with the other components of SDs irrespective of the solvent or melting method or whether it is an SESD or NSESD. The approach of introducing pH modifiers into the system is important because mixing SD with pH modifiers separately (physical mixture) would not yield an effective enhancement of the dissolution rate as much as adding pH modifiers to the SDs (34). The highest drug solubility can be obtained in the latter because the drug is already soluble in pH_M-modified SDs in the SD preparation before reaching the dissolution media. Enhanced drug dissolution from pH_M-modified SDs also depends on the solubility of pH modifiers: pH modifiers possessing low solubility are better able to maintain the pH_M for an extended period that is sufficient for drug dissolution in the medium (35). In addition to optimization of the pH_M of the SD for controlled drug solubility, structural behaviors and intermolecular interaction among the SD's components also affect the enhancement of drug dissolution by inducing the carrier to reduce or diminish drug crystallinity or by preventing the recrystallization of an amorphous SD system (32–34). Therefore, understanding the pharmaceutical mechanisms of pH modifiers in SD systems, including the correlation among potential changes in drug crystallinity, pH_M control, the release rate of pH modifiers and the enhanced dissolution of poorly water-soluble drugs, is essential for a successful strategy.

CONTROLLED RELEASE USING HYDROPHILIC AND HYDROPHOBIC MATRICES: UTILIZATION AND MECHANISM

Despite the widespread application of polymers in designing oral formulations and manufacturing drug devices for controlled drug delivery, few reports describing controlled release materials and their mechanisms for controlled drug release are available. Information on the properties and mechanisms is summarized herein to give the reader a general but deep understanding of the most commonly used materials in controlled drug delivery systems. The CR systems are mainly matrix systems in which active and inactive ingredients are homogenously mixed in the dosage form (36–39). Matrix systems are the most commonly used oral CR technology because of pharmaceutical advantages such as economic benefits, the relative simplicity of process development and scale-up procedures, and the ability to load an appropriate drug with a wide range of physical and chemical properties. From this type of dosage form, drug release occurs by mechanisms of leaching, diffusion, or

erosion, depending on the property of matrices such as porosity or swelling (1). Pharmaceutical excipients in the formulation facilitate drug release by absorbing aqueous fluids into the tablet. Based on rate-controlling materials, matrix systems can be divided into two categories: hydrophobic and hydrophilic matrices. The properties of materials should be carefully considered because they reflect the drug release mechanism. For example, for hydrophilic matrices, the drug release rate commonly decreases as the proportion of the material in the matrix increases because of a greater degree of hydration with simultaneous swelling and a corresponding lengthening of the drug diffusion pathway. Hydrophobic matrix systems are less commonly applied in controlled drug release when compared to hydrophilic systems because they are the only systems in which the use of polymer is not essential to the controlled drug release function (40). It has also been suggested that the incorporation of a soluble ingredient should be added into such hydrophobic matrices to modulate the release of practically insoluble drugs. However, the use of a hydrophilic matrix alone to extend the release of highly water-soluble drugs is sometimes restricted due to the rapid diffusion of the dissolved drug through the hydrophilic gel network. It is essential to include hydrophobic materials in the matrix system in such cases (41). Table I summarizes the rate-controlling matrix-forming materials most commonly used in CR-SDs.

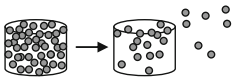
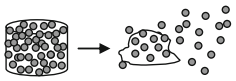
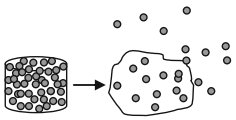
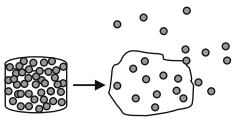
Hydrophobic Matrices

The presence of hydrophobic matrices helps to maintain the physical dimensions of the formulations during drug release. Generally, hydrophobic matrix systems are not suitable for poorly water-soluble drugs because the concentration gradient is too low to render adequate drug release, which probably would be a potential risk within the gastrointestinal transit time. Obviously, the hydrophobic matrices are water-insoluble materials in nature, such as ethylcellulose (EC), methacrylate copolymers, Kollidon® SR, or lipophilic compounds such as waxes, glycerides, all of which are slightly or non-swellable.

Non-lipid Based Matrices

One note should be pinpointed herein that EC is not actually a hydrophobic polymer. The research of Agrawal *et al.*, 2003, indicated that although EC is not water soluble, it shows some physical interaction with water, therefore, defining EC as a relatively hydrophobic polymer (42). Generally, it is used extensively as a coating material and, less commonly, as a binder, and it is used as a matrix-forming material in the preparation of matrix-type CR tablets and CR-SDs (43). Although EC does not exhibit swelling, its compactibility becomes a key factor in such systems because release kinetics would depend largely on the porosity of the hydrophobic compact. Despite its insolubility, the polymer can take up water because of its hydrogen-bonding capability with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer (44). The preparation of these dosage forms requires several unit operations in some cases, and it is especially noteworthy that many of these processes require solubilization of all or part of the EC using an organic solvent, which raises some environmental concerns (45). Direct compression is a preferred method of manufacturing CR tablets. Tablet hardness, the particle size of the polymer, and the viscosity grade are factors directly affecting the drug release rate. Tablet hardness has a stronger impact on the dissolution half-life than viscosity grade. Lower viscosity grades induce more compressible dosage forms, allowing for a wider range of tablet hardness and, thus, of dissolution rates (46). Among the various viscosity grades of EC, a 10 cps viscosity grade is highly compressible and produces a harder tablet (47). Tablet hardness is limited by the compression force at a given viscosity grade (48). One of the major problems in hydrophobic matrices is the decreased terminal release rate. EC-based matrices with erosion properties can reduce this problem (49). For water-soluble drugs, simple diffusion appears to be the mechanism of drug release from an EC matrix tablet, as with pseudoephedrine hydrochloride at 12.5–25% drug loading, in which the data are described by the Higuchi equation (50). Meanwhile, the release of slightly soluble theophylline or practically insoluble indomethacin at 50% or 25% drug loading, respectively, occurs by diffusion with polymer relaxation and erosion contributions (46). Pather *et al.* also investigated an EC matrix tablet containing theophylline in which a release profile resembling the zero-order model has been reported (49). The drug release mechanism from directly compressed EC tablets has also been elucidated by Neau *et al.* for xanthine derivatives such as theophylline, caffeine, and dyphylline, which have solubilities of 8.3 to 330 mg/ml at 25°C (47). At high drug loading, these drugs are released by a diffusion mechanism with a rate constant that increases with increased solubility, whereas at low drug loading, polymer relaxation becomes a release mechanism. However, the contribution to drug release is less pronounced as solubility decreases in the case of theophylline. Despite several advantages, such as flow and cohesion that are suitable for compaction with high-dose drugs exhibiting poor flow and/or poor compactibility as well as increased content uniformity in the tablets with low-dose drugs, the preparation of matrix-type tablets by aqueous wet granulation has not been successful using coarse EC. However, fine EC offers the potential to improve the characteristics of wetted

Table I Rate-Controlling Materials Commonly Used in Controlled Release Solid Dispersions

	Polymers	Prominent Properties	Comments	
Hydrophobic matrices	Ethylcellulose	Absence of polymer swelling ability but the compactibility is a key factor. In spite of insoluble property, the polymer can take up water.	Typically used in combination with water-soluble actives and/or water-soluble excipients.	
	Methacrylate copolymers	Swellability and permeability, pH-dependent/independent properties depending on acidic, alkaline and neutral groups.	Flexible combination of various polymers enables to achieve the desired drug release profile.	
	Carnauba wax, Compritol, Precirol, etc.	Good stability at various pH and moisture levels, chemical inertness against other materials, excellent flow properties and effective retardation.	Easy processability of low-viscosity melts, thus obviating the need for organic solvents.	
Hydrophilic matrices	Cellulose ethers (hydroxypropyl methylcellulose-HPMC, hydroxypropyl cellulose-HPC, hydroxyethyl cellulose - HEC)	Varied gelation behavior based on viscosity and extent of substitution. Erosion, swelling behavior, water uptake correlated well with hydrophilicity (HEC > HPMC > HPC).	HPMC is the first choice for the formulation of hydrophilic matrix systems. Higher viscosity for HPMC compared to HPC and HEC at comparable molecular weights.	
	Xanthan gum	An anionic polyelectrolyte polymer whose swelling is strongly influenced by the ionic strength and buffer concentrations.	Drug diffusion is faster in hydrated HPMC than in xanthan gum matrices.	
	Sodium alginate	Good membrane forming, pH-sensitivity, biodegradability, capability of gel formation and cross-linking.	When alginic acid is formed, it could stimulate the tablet disintegration because it is insoluble but swellable in water.	
	Carbopol	Mucoadhesive, high sensitivity to the pH of the medium, capability of good gel-forming and cross-linking.	Surface gel formation does not occurred.	
	Polyethylene oxide (PEO)	Referred as the limited swelling hydrophilic matrices, mucoadhesive property which may assist in prolonging the gastric residence time.	The degree of swelling of PEO is higher than that of HPMC.	

powder blends via its large surface area, which permits water binding. Agrawal *et al.* proposed the applicability of fine EC to the preparation of tablets by an aqueous wet granulation technique with both nonionizable and ionizable drugs (45). Fickian diffusion is the primary release mechanism, and polymer relaxation is a secondary release mechanism for the release of both nonionizable and ionizable drugs.

Additionally, methacrylate polymers have been widely used as tablet coatings and as retardants of drug release in sustained-released formulations (51). The polymers receiving the most attention are highly permeable Eudragit® RL and less permeable Eudragit® RS, which have different contents of quaternary ammonium groups. Both of them are neutral co-polymers of poly(ethyl acrylate-co-methyl methacrylate) and trimethylaminoethyl methacrylate chloride and are insoluble in water and digestive juices. The swellability and permeability of both of these acrylic polymers induce drugs embedded in their matrices to be released by diffusion (52). The permeability of the drug

through Eudragit RS and/or RL is independent of the pH of the digestive tract, and the degree of permeability depends on the relative proportion of quaternary ammonium groups, which is 10% in Eudragit RL and 5% in Eudragit RS (53). Eudragit RL and RS are sensitive to a counterion interaction through the polymer's quarternary groups. In their research, Wagner and McGinity investigated the permeability of the Eudragit RS 30 D films as influenced by the anionic buffer species of the dissolution media with special emphasis on the chloride ion exchange of the polymer (54). Other research from other groups also proved this property of the Eudragit RL, such as the investigation on diltiazem HCl release from beads coated with Eudragit RL and RS whose hydration was affected by buffer species and strength because the chloride counterions of the quaternary groups were exchanged with the anionic buffer species during the dissolution study (55). Glaessl *et al.* characterized the interaction between metoprolol tartrate and Eudragit RL and Eudragit RS, which significantly affected the mechanical strength and the Tg of the polymeric network (56). Matrix tablets can be prepared via direct compression with Eudragit® powders, such as with Eudragit® S100 and Eudragit® RSPO, or wet granulation with aqueous polymer dispersions, such as with Eudragit® L 30D-55 and Eudragit® NE 30D. Wet granulation is particularly suitable for high-dose, readily water-soluble active agents. Because polymethacrylates perform the dual function of delayed matrix former and binder, the addition of further excipients to increase the strength of compressed tablets is rarely required. The release of drugs from these matrix tablets initially occurs preferentially by diffusion through pores, whereas subsequently, the tablets are eroded and disintegrated slowly. The kinetics often follow the laws described by Higuchi (57–59). Important factors influencing drug release are the particle size, the dose and solubility of the drug, the type and quantity of the matrix former, and the porosity and disintegration behavior of the tablets. Eudragit® RS 30D and Eudragit® NE 30D as methacrylic acid ester polymers are utilized to prepare matrix tablets, as they are able to slow drug diffusion because they are slightly swellable and permeable. Their permeability is comparable, but Eudragit® NE 30D presents the advantage of lacking any plasticizer, in contrast to RS 30D, which requires 20% by weight of plasticizer like triethylcitrate (49,60). Another study investigated different pH-dependent (Eudragit L100, S100 and L100-55) and pH-independent (Eudragit RLPO and RSPO) polymer combinations on theophylline in extended-release matrix tablets with the recommendation that all the employed types of Eudragit are suitable as matrix-forming agents (61). A constant 1:1 (*w*/*w*) drug/polymer ratio and a mixture of pH-dependent Eudragit L100 and pH-independent Eudragit RLPO at 0.7:0.3 *w*/*w* shows highly reproducible drug release profiles with almost zero-order kinetics, and it permits 100% drug release after 360 min. Simple blending is more effective than the SD technique, which not only does not improve the reproducibility of the release data but also unexpectedly causes a marked decrease in the drug release rate.

In addition to EC and methacrylates, a polyvinyl acetate-based excipient, commercial product named Kollidon® SR, should not be neglected herein. The excellent flowability and compressibility of Kollidon SR makes it particularly suitable for the manufacture of sustained release tablets using direct compression. Actually, this product is also comprised of a hydrophilic component, polyvinyl pyrrolidone, at 19% (*w*/*w*) (62). However, due to the superior amount of the water-insoluble polyvinyl acetate (80% *w*/*w*), even a highly water-soluble drug like caffeine could obtain a sustained release for 16 h (63). This specific ratio gives Kollidon® SR a unique character of maintaining tablets' geometric shape until the end of dissolution testing. The minor water-soluble part, polyvinyl pyrrolidone, is responsible for pore formation causing diffusion controlled release mechanism of Kollidon® SR-based matrices. Moreover, because it has no ionic group rendering the polymer inert to the drug molecule, Kollidon® SR shows a pH-independent release profile from these sustained release matrices (62,64).

Lipid-Based Matrices

Other inert and non-swellable materials to prepare matrices are lipophilic materials that provide several advantages, including good stability at various pH and moisture levels, chemical inertness against other materials, excellent flow properties and effective retardation of drug from the matrix (65). The major advantage of these materials *versus* polymers is the easy processability of low-viscosity melts, which obviates the need for organic solvents (66). A rigid lipid-based matrix can be made by simply heating. However, drugs are sometimes unstable under heating or are not sufficient for sustained effects, especially for highly water-soluble drugs, so manufacturing conditions have to be carefully specified to obtain the matrices with the desired properties (67). Generally, different processing methods, such as dry blending (direct compression), wet granulation, melt granulation and extrusion spheronization, have been proposed for forming a lipid-based matrix system (68–70). When a non-swellable lipophilic material is used as a matrix in CR formulations, merely mixing the ingredients is not enough; rather, drug and excipients have to be formulated into an SD in which the physical mixture of drug and lipidic materials is first melted and then granulated through a sieve (71,72). The homogeneity of the drugs in the matrix is essential for controlling drug

release. Sintering, defined as the bonding of adjacent particle surfaces in a mass of powder or in a compact by application of heat, can further retard drug release by decreasing the porosity of the matrix, and this is important in manufacturing processes (73). Drug release from a lipid-based matrix with or without heat treatment is best described by the Higuchi equation (73). Heat treatment causes the lipidic materials to melt, redistribute, coat the drug and diluents and form a network structure. Some common lipidic materials used as CR matrix include waxes such as carnauba wax, beeswax, paraffin, and glycerides such as Compritol and Precirol. Compritol 888 ATO, composed of glyceryl behenate, is a waxy material with a low fusion point originally introduced as a lubricant for tablets that has recently seen extensive application as a sustained-released excipient (74). The material has been used as a hot-melt coating agent or CR agent in matrix tablets to prolong drug release (74,75). Bodmeier *et al.* investigated lipid-based microparticles by a melt dispersion technique for water-insoluble drugs such as ibuprofen, ketoprofen, indomethacin, and hydrocortisone using carnauba, paraffin, beeswax, Precirol AT05, and others (66). To obtain the final dosage form, the microparticles can be compressed into tablets, which disintegrate into the original microparticles upon contact with gastrointestinal fluids, or can be filled into hard gelatin capsules. The type of lipidic material, the rate of cooling, and the temperature of the aqueous phase have no significant effect on the drug loading because of the low solubility of the drug in the external aqueous phase. The drug release is controlled by particle size and the hydrophobicity of the lipidic material. Bodmeier *et al.* (66) found that drug release increases with decreased microparticle size and is fastest from the less hydrophobic Precirol AT05, followed by (in order of hydrophobicity) beeswax, carnauba wax and paraffin wax microparticles. During transit through the gastrointestinal tract, those inert materials whose porous matrices do not disintegrate but remain intact have skeletons that can be recovered in the feces. The major drawbacks of most of the inert matrices are the inherent first-order drug release, poor direct compression characteristics and problems related to cleaning agglomerations on the equipment that form during preparation.

Another group that should be listed in the lipid-based matrices is sugar esters, although they control drug release via gelation and swelling behavior. This mechanism is facilitated by various hydrophilic–lipophilic properties of these esters. Sucrose esters, the most commonly used in sustained release dosage forms, are esters of sucrose and fatty acids derived from edible fats and oils non-toxic, biodegradable and have hydrophilic–lipophilic balance (HLB) values ranging from 0 to 16 (76). Slow drug release was observed from microcrystalline cellulose matrix tablets containing sucrose esters with a HLB value of either 1 or 15, regardless of two fatty acid types, i.e., stearate and palmitate, whereas tablets containing sucrose esters with a HLB value of 7 had a less sustained release effect (77). Recently, Chansanroj and Betz investigated sucrose esters as novel controlled release agents for oral drug delivery matrix tablets prepared by direct compaction (78). Sucrose stearate with HLB values ranging from 0 to 16 was systematically tested in the study, showing that various hydrophilic–lipophilic properties of the esters affected tableting properties, drug release rate and release mechanism. Increasing hydrophilicity resulted in an increase in the porosity, elastic recovery and tensile strength of the matrix tablets as well as facilitating swelling behavior that retarded the drug release rate.

Last but not least, knowledge of digestion and absorption of lipids in the gastrointestinal tract is indispensable in the research and development of lipidic drug delivery systems for oral administration. The digestion process requires several enzymatic components for the conversion of nonpolar, insoluble lipids into water-soluble and absorbable products (79). Therefore, physicochemical properties of the lipidic materials should be determined because it could explain the reason why paraffin wax is excreted in the feces, whereas glycerides, due to less hydrophobicity, are digested by gastric and pancreatic lipase and co-lipase (80), or sucrose esters can be enzymatically hydrolysed to sucrose and fatty acids prior to intestinal absorption or excreted in feces, depending on the degree of esterification (81), for instance.

Hydrophilic Matrices

Hydrophilic matrix systems (polymeric matrix tablets or polymer powders in hard capsules) dominate today's market of oral CR products due to their beneficial characteristics of controlled drug release as well as their more versatile processing and scale-up compared to other CR systems. The hydrophilic matrices are formed by the rate-controlling hydrophilic polymers that would swell upon contact with the aqueous solution and form a gel layer on the surface of the system via water uptake (82). Within the hydrated surface layer of the matrix, the core remains dry, acting as a non-releasing reservoir of drug and polymer. The speed of the initial water uptake and the conversion to a viscous layer is important to evaluate the control and mechanisms of drug release from matrices. The hydrated gel layer thickness determines the diffusional path length of the drug. When the matrix swells, the diffusion path is lengthened, increasing the time required to diffuse the drug out of the matrix. As the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer,

leading to disentanglement and erosion of the surface of the matrix. Water continuously penetrates toward the core tablet until the tablet has dissolved (82). The drug release mechanism is also governed by drug solubility. Controlling drug release is complicated because the process compromises the release of drug from porous, swelling and eroding matrices, which involves the hydration process. Swelling facilitates drug release through Fickian diffusion, whereas erosion results in anomalous diffusion, and these have been reported as case I (square root of time release) and case II transport (zero-order release) (83). It is assumed that water-soluble drugs are released primarily through diffusion through the gel layer, and an initial burst release may occur due to the presence of the drug on the surface of the matrix. On the other hand, the release rate is controlled by the erosion process for drugs of low water solubility. It has to be considered that the matrix geometry noticeably effects the controlled drug release (84). For example, if the tablet diameter is quite larger than its thickness, drugs have a tendency to dissolve before polymers erode from the dosage form. However, for insoluble molecules, drug particles may not dissolve completely after polymers have eroded. The dual release processes induce hydrophilic matrices more prone to meet polymer erosion, thereby modulating further release control of the insoluble compounds. For drugs with pH-dependent solubility, it is not likely that pH-independent release can be achieved even if the rate-controlling polymer is pH independent. Drug particle size is also an important factor influencing drug release, especially for moderately soluble drugs (85). For a productive extended drug release, it is essential that polymer hydration and surface gel layer formation be quick so that immediate tablet disintegration and premature drug release are prevented. For this reason, polymers for hydrophilic matrices are usually supplied in small particle sizes to ensure rapid hydration and consistent formation of the gel layer on the surface of the dosage form. At the same time, the larger particle sizes would dissolve less readily and therefore be more prone to erosion at the matrix surface (86). Another factor affecting the drug release rate is the polymer content: an increase in polymer content results in increased viscosity of the gel matrix, causing a reduction in the effective diffusion coefficient of the drug (87,88). Increasing polymer concentration provides more particles to cover the tablet surface and reduce the polymer-free areas, which could reduce the burst release of drug. However, decreased drug release rate with increased polymer content is not always observed (87). Other factors, such as differences in water penetration rate, water absorption capacity and swelling, which result from changes in polymer content, play a role in modulating drug release. Moreover, it is unlikely that a change in the diffusion coefficient is entirely responsible for a change in drug release rate. Manufacturing processes such as direct blending or granulation usually do not influence product performance significantly. However, weakened gels tend to be more sensitive to environmental variables in the gastrointestinal tract, such as shear and ionic strength, leading to potentially less robust performance (89). In most cases, the choice of polymer, filler type and their levels determine the drug release kinetics. Some strategies have been investigated to further modulate drug release from these matrices, including using other polymers, restricting the swelling characteristics, or using compression coating with another hydrophilic polymer or insoluble film coating (90). Although the formulations may vary in design and composition, they all should achieve similar CR profiles both *in vitro* and *in vivo*.

Because cellulose ethers play an important role in the formulation of hydrophilic CR systems, several researchers have sought to examine their physicochemical properties correlated with their effects on modulation of drug release. The viscosity of water-soluble cellulose derivatives depends on the molecular weight of the cellulose derivative, solute concentration and temperature. Due to its worldwide use in the area of controlled drug delivery systems, Hypromellose is the most important cellulose derivative in this field. Short for hydroxypropyl methylcellulose (HPMC), it is a semisynthetic, inert and viscoelastic polymer found in numerous commercial products and is frequently used as a controlled-delivery component of hydrophilic matrices in oral medicaments. HPMC is available in several grades on the market based on viscosity and the extent of substitution, which alter the gelation behavior, allowing the drug release rate to be modified. The substitution type is specified by appending a four-digit number after "HPMC," such as HPMC 2208 (K type), HPMC 2910 (E type) and HPMC 2906 (F type), in which the first and the second pairs of digits refer to the approximate percentage of methoxy groups and hydroxypropoxy groups, respectively, calculated from the dried form (53). HPMC K types are considered to hydrate faster than E, F or A types. Additionally, the polymer is classified by typical viscosity values as 2% (*w/v*) aqueous solutions—for instance, HPMC K4M and HPMC K15M, referring to nominal viscosities of 4,000 and 15,000 cps, respectively. A unique functional property of HPMC is the phenomenon of thermoreversible gelation when dissolved in water. That is, they can form gels when the temperature reaches a critical level due to hydrophobic interactions between molecules containing methoxy groups, which consequently stabilize intermolecular hydrogen bonding (91), and the gel re-dissolves on cooling (92). Meanwhile, the polymer precipitates above this temperature. Cloud points and thermal gelation are two important parameters when considering this property of HPMC. The critical temperature of HPMC solutions, which may be described as a cloud point, is inversely related to both the concentration of HPMC

solution and the methoxy group within the HPMC molecule. The minimum value of the cloud point, if any, is used to explain the poor performance of the matrix in maintaining integrity on exposure to water. The temperature at which the association within polymer occurs, leading to an increase in viscosity before complete dehydration, is called the thermal gelation temperature, which is affected by the type of cellulose, the polymer concentration and the presence of ionic materials in solution. A report from Mitchell *et al.* on propranolol hydrochloride challenges the principle that the substitution type may affect the release of soluble drugs. Their water uptake study indicated that uptake may not be significantly different among various types of HPMC, resulting in drug release rates being independent of the substitution type (93). Drug release profiles from HPMC hydrophilic matrices are generally first-order for highly soluble drugs or zero-order for insoluble drugs. Usually, small-particle-size fractions of HPMC are believed to be essential in the HPMC-based CR delivery systems. Nevertheless, Mitchell *et al.* indicated that larger HPMC particles have higher initial hydration rates compared to smaller particles. Hence, it is postulated that the increased release rates from the HPMC matrices are due to the relative lack of the polymer (94). HPMC polymers generally have good compressibility, resulting in tablets with high mechanical strength. High-molecular-weight grades of HPMC undergo less plastic flow than low-molecular-weight grades, so the former require higher pressure to deform. For direct compression, the inclusion of direct compression excipients may facilitate the formulation of HPMC-based matrix tablets with acceptable mechanical properties. In wet granulation, because HPMC itself has excellent binder properties when hydrated, the addition of a binder may not be necessary. Nevertheless, one drawback of HPMC is the high shear sensitivity reaching with some instability (95). Bajdik *et al.* did some preformulation studies in the research of wetting effect of powder mixture on the preparation of hydrophilic matrix granules with high-shear granulator, revealing that HPMC without other components (Mix100) is not appropriate for high-shear granulation (96).

In addition to HPMC, other non-ionic cellulose ethers commonly used in hydrophilic matrix systems are hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC). Generally, these polymers have the same properties as HPMC, with various molecular weights and degrees of substitution. The following descriptions only discuss the differences between HPMC and the other polymers. Erosion and swelling behavior both correlate with hydrophilicity; in descending order, HEC > HPMC (type 2208) > HPC (97). The hydrophobic methoxy groups of HPMC undergo hydrophobic association, which is not affected by the molecular weight of the polymer but manifests as higher viscosity for HPMC compared to HPC and HEC at comparable molecular weights. Accordingly, the gel strength obtained with HPMC is clearly superior. Generally, for highly soluble drugs, the polymer hydrophilicity and molecular weight have negligible impacts on drug release, but the extent of erosion and swelling of HPMC do affect it. Additionally, drug solubility causes a rapid influx of water, resulting in a large osmotic pressure generated in the matrix of these highly soluble drugs. However, increased polymer concentration, varying surface area/volume ratio, and the application of hydrophobic coatings are additional strategies to modulate the drug release profiles in such cases. As drug solubility decreases, polymer swelling and matrix erosion processes increasingly dominate the drug release mechanism. Water uptake is small for drugs with very low solubility compared to soluble drugs, but it correlates well with hydrophilicity (HEC > HPMC > HPC) and molecular weight. However, there is a poor correlation between tablet swelling and drug release. Drug release depends directly on the tablet matrix erosion rate, indicating that drug matrix could meet the rate-limiting step of dissolution. HPMC, despite its higher hydrophilicity relative to HPC, does not follow this rule, as the hydrophobic association between methoxy substituents results in increased erosion resistance. Meanwhile, molecular weight variation is a more effective tool in modulating release rates for HPC- and HEC-based systems. For the poorly water-soluble drug dissolution, the low molecular weights of HPC and HEC provide nearly complete release in physiological time periods, whereas the other grades of HPC and HEC including the low molecular weights of HPMC are unable to achieve sufficient release in physiological periods due to their low erodibility. Recently, some research on HPMC which has been notified by a group of scientists from Sweden shows that the same USP quality of HPMC gives very different release and erosion rates (98,99). For proving that the heterogeneous substituent pattern facilitated hydrophobic interactions that increased the viscosity and therefore affected the polymer release rate to a major extent from hydrophilic matrix tablets (98), they prepared polymer tablets from three heterogeneously substituted HPMC batches of the same substituent (2208) and viscosity (100 cps) grade and characterized fractions of both the dissolved polymer and the tablet residue collected from the dissolution bath. Actually, in a previous publication in 2009 (99), the Swedish scientists showed that different properties in solution can be achieved by altering the substituent pattern of two HPMC batches of the same commercial grade through lots of analyses of clouding curve *versus* chemical heterogeneity, properties of phase-

separated solutions, etc. In conclusion, they recommend that both users and producers must be aware of the polymers' complex structure because they generate a wide variety of solution properties for the same material and even the same commercial grade and, hence, emphasize the importance of careful characterizations of the parameters related to the functionality of cellulose derivatives in order to understand the polymers' behaviors in different applications.

Furthermore, non-cellulosic hydrophilic polymers used to fabricate matrices include water-soluble/swellable polysaccharides (xanthan gum and sodium alginate), acrylic acid polymers (Carbopol) and high-molecular-weight polyethylene oxide (PEO). Sodium alginate is a widely used water-soluble polysaccharide that is suitable for CR applications for the release of both hydrophilic and hydrophobic drugs and charged solutes due to its good membrane-forming properties (100), pH sensitivity, gel formation capability, and ability to regulate drug release by controlling swelling and cross-linking (101). The nature property of alginates makes them an attractive material with biocompatibility, but the biodegradability is questionable since many studies indicated no, very slow or unpredictable degradation of alginates (102,103). The gel strength of the polymer can be improved by the presence of the Ca^{2+} ions for cross-linking due to ionic interaction and intramolecular bonding between the carboxylic acid groups located on the polymer backbone and the cations (104). Many different grades of sodium alginate that are commercially available for designing CR dosage forms vary in their particle size, molecular weight and chemical composition, and they determine the physical properties of the gel formability (105) and influence drug release behavior. High-viscosity alginate has a larger particle size and hydrates slower, leading to slower gel barrier formation and, thus, faster erosion or dissolution of alginate particles (86). The pH of the medium is also very important; for instance, changes of pH from 6.8 to 1.2 affect polymer hydration and gel rheology due to the ready interconversion of carboxylate anions of sodium alginate to free carboxyl groups of alginic acid, as the concentration of hydrogen ions increases (106). When alginic acid is formed, it can stimulate tablet disintegration because it is insoluble but swells in water or high pH solution. CR matrix tablets composed of sodium alginate can be prepared by direct compression (107,108), granulation (109,110) and compression coating (109,111) or spray coating (112). However, work done on alginate-based matrix tablets is still limited. Liew *et al.* investigated 17 grades of sodium alginate with different particle size distributions, viscosities and chemical compositions in preparing matrix tablets at various concentrations to screen the factors influencing drug release from such matrices (113). Their results show that particle size is important because reduced particle size results in slower drug release and diminishes the initial burst effect. Moreover, the effect of increasing alginate concentration is greater with larger alginate particles, higher viscosity slows drug release in the buffer phase but enhances it in the acid phase, and high M-alginate content might be more advantageous than high-G-alginate in sustaining drug release. They also showed that different grades of alginate do not influence matrix swelling significantly in acidic medium, but they do in neutral medium. In medium below pH 3, the hydrated layer formed around the tablets is not viscous or adhesive in nature but has a tough and rubbery texture, probably due to the conversion of sodium alginate to alginic acid at pH 1–2. The presence of ammonium or calcium salts induces tablet disintegration in acidic medium. The incorporation of sodium bicarbonate, resulting in a constant basic environment, which prohibits the conversion of sodium alginate to alginic acid and allows calcium ions to partially form a gel with soluble sodium alginate, has a similar effect on swelling and erosion in both media. Moreover, the morphology of alginate matrix tablets containing sodium bicarbonate in acidic medium includes less lamination and fewer cracks compared to the tablets without sodium bicarbonate. The integrity of the matrices is diminished during dissolution, and the extent of deformation is greater at higher alginate concentrations because the extent of matrix swelling increases due to greater liquid imbibitions, increasing the pressure within the matrix, which is released by matrix deformation.

Another polysaccharide is xanthan gum, which is less commonly used than sodium alginate but is able to absorb water at a fast rate, which is consistent with its fast swelling rate. Thus, it has the ability to hydrate rapidly, resulting in a long diffusional path to retard the drug release rate. Some important pharmaceutical and economical advantages of xanthan gum over HPMC are the absence of initial burst release, higher drug-retarding ability, the possibility of zero-order release kinetics and better flowability (114). Because the erosion rate is relatively moderate compared to the swelling rate, it yields a sufficient drug dissolution rate. Swelling is strongly influenced by the ionic strength and buffer concentrations, whereas drug release is affected by drug solubility, which is described by a direct relationship with swelling of the polymer matrix for insoluble drugs and an inverse relationship for soluble drugs (115). A careful balance between the diffusion and erosion mechanisms is required to optimize drug release toward zero-order kinetics. Fickian diffusion is dominant during the first half of the dissolution period, whereas erosion predominates during the latter half, facilitating an approach toward zero-order release. If drug diffusion outwards through the hydrated gel is slower than the permeation of water inwards, the swelling effect is more pronounced (116). Regarding drug and polymer content in the matrix, the

penetration rate is lowest with the highest drug content. Moreover, the hydration and swelling of matrices at a high gum content may be slow but will finally reach its maximum value. The hydrated regions are highly porous because the dissolved drug does not inhibit the swelling process. Bonding between the polymer network chains is rather reduced as they become separated, with consequent loss of matrix integrity (116).

The other hydrophilic polymers are Carbopol and PEO, which are not polysaccharides or celluloses types. Carbopol is a cross-linked polymer of acrylic acid with a high molecular weight that forms a hydrogel in aqueous solutions, depending on the degree of hydration of the carboxyl group in the polymer (117). Despite many advantages as a candidate for an extended-release tablet matrix, such as a good gel-forming and mucoadhesive properties, there are few reports on the application of Carbopol to CR dosage forms. This might be due to the ionic nature and high sensitivity of Carbopol to the pH of the medium (118). It's widely known that Carbopol has an especially strong affinity for divalent cations such as calcium and zinc (119,120). Therefore, the drug release rate from Carbopol-based matrices is difficult to control and is correlated with *in vivo* drug absorption (117). Carbopol is a cross-linked polymer, so it is not water-soluble but swells on hydration and forms a gel layer. Accordingly, in contrast to HPMC, whose swelling behavior is due to the hydration of the polymer, leading to relaxation of polymer chains and subsequent entanglement of these chains (cross-linking) to form a viscous gel, surface gel formation by Carbopol occurs due to the formation of various microgels made up of many polymer particles. In contrast, PEO is a non-ionic, water-soluble resin that is available in a variety of molecular weight grades. PEO forms limited-swelling hydrophilic matrices (121). The main difference between these and systems based on cellulose ether polymers is the drug delivery mechanism. Drug diffusion is controlled by the penetration rate of solvent in the matrix. The advantages of these systems include the possibility of incorporating drugs with faster degradation, zero-order release kinetics, and easy preparation. However, disadvantages have been reported; for instance, zero-order release kinetics are not evident when the drug is in a higher concentration, and relatively high temperatures in some preparation processes can promote drug degradation (121). The release of dissolved drugs from the system is relatively quick because the continuous swelling can promote its solubilization. If this occurs, controlled drug delivery is not achieved. For the low-molecular-weight PEO, the synchronization of gel layer thickness occurs earlier as compared with the high-molecular-weight PEO, which swells to a greater extent. Moreover, drug release from PEO is controlled more by polymer swelling than to dissolution, leading to a progressive decrease of the drug's diffusive conductance in the growing swollen layer and hence to a non-constant release induced by the prevailing diffusive control. Conversely, drug release from the low-molecular-weight PEO is strictly related to the polymer dissolution mechanism (122). As compared to HPMC, the degree of swelling of PEO is higher (123). A study on PEO tablets for some drugs with varied solubility showed that the release of diclofenac sodium (2.5% solubility in water) is characterized by non-Fickian kinetics, whereas as drug solubility decreases below 1% (theophylline and salicylic acid), drug release is slow as a result of the longer dissolution time of the drug ion in the matrix. As drug solubility decreases further below 1,000 mg/L, the drug dissolution becomes a dominant process in controlling the drug release from PEO tablets (124). The drug release rate is also suggested to be a function of drug loading. For instance, drug release is controlled at a zero-order rate by the dissolution of the drug at high loading (39%) from tablets containing PEO of molecular weight 4×10^6, whereas at low loading (20%), drug diffusion through the swollen gel layer is the governing release mechanism. The compression force applied during the manufacturing process, the pH of the release medium and the stirring rate do not significantly affect the drug release behavior. Hot-melt extrusion is also a common method for PEO to form a matrix.

CLASSIFICATION AND PREPARATION OF CR-SD

The term "CR-SD" evokes CR systems bearing SDs, so the preparation of these systems should focus on the approaches and functions related to SD and CR dosage forms. Fig. 1. depicts manufacturing approaches for a typical CR-SD with the corresponding physicochemical and biopharmaceutical characterization.

Traditional Methods

Regardless of the type of CR-SDs, solvent and melting methods are the two basic manufacturing processes used to prepare SDs. In the solvent method, SDs are prepared by dissolving accurately weighed amounts of carrier and drug in an organic solvent (125), which will then be evaporated after a complete dissolution of drug and carrier. Subsequently, the solid mass is ground and passed through a sieve with a suitable mesh size. For the melting method, the preparation steps are usually carried out as follows: the mixture of drug and carrier is completely melted at a certain temperature to obtain the final uniform melt, which is then cooled at room temperature or, more frequently, at a freezing temperature, followed by pulverizing and sieving. The SD products are usually stored with silica gel or under pressure in desiccators. Depending on the SD preparation,

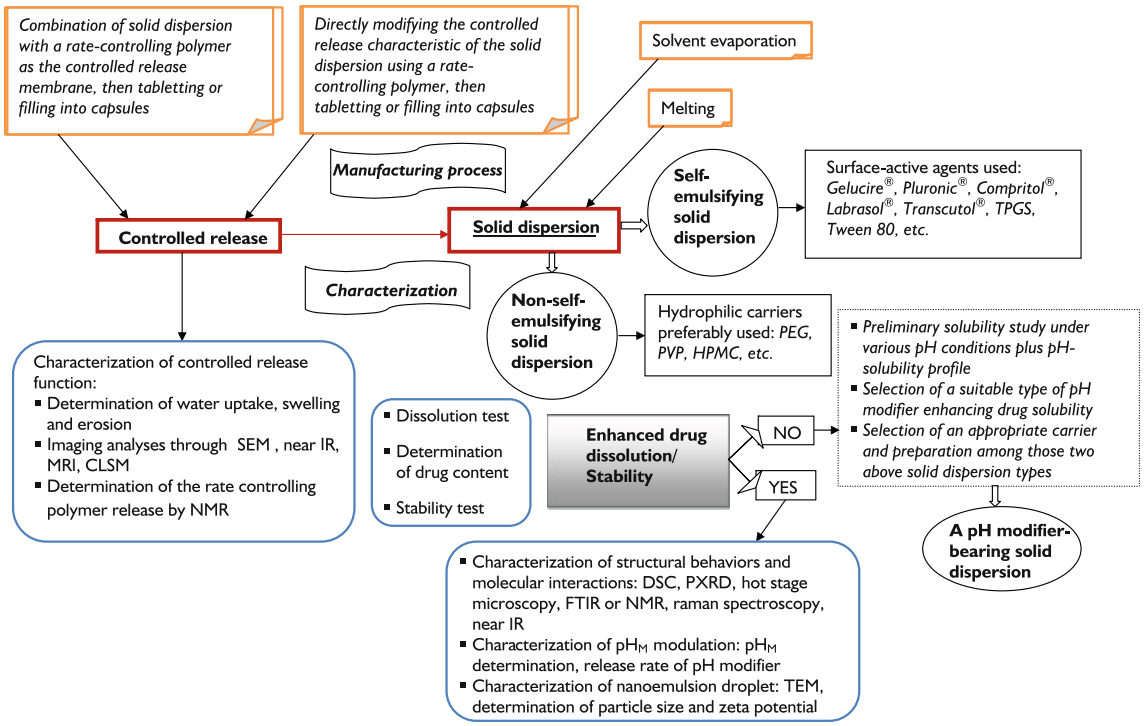


Fig. 1 Scheme of preparation and characterization of a typical controlled-release solid dispersion.

there are some matters related to each specific method, such as the type and amount of solvent suitable to dissolve both carrier and drug and conditions (equipment such as ovens and incubators at room temperature or high temperature) for solvent evaporation, the selection of sufficient temperature to completely melt the mixture and the method of hardening the melt so that it can be ground for subsequent formulation into powder-filled capsules or compressed tablets, depending on the nature of the drug and the stability of the system. Organic solvent is used alone or in some proportion with water, based on the solubility of the carrier, to dissolve the carrier and drug. Ethanol is commonly used and highly recommended because of the low risk of harm to the environment and personnel. Minimizing the temperature and volume of organic solvent is necessary to obtain a productive SD. Other approaches based on those two basic methods have been suggested: gentle heating can be used to increase the solubility of components in the solvent method (126), or only the drug can be dissolved in the organic solvent, followed by adding the solutions to the melted carriers (127). Although the SD technique is commonly used to enhance the dissolution properties of poorly water-soluble drugs using hydrophilic polymeric carriers as dispersing agents (7), several studies on SDs have referred to "CR-SDs" using water-insoluble carriers such as EC (128), Eudragit (129), and Compritol (74) to produce sustained-release pharmaceutical forms of highly water-soluble drugs. By using SDs containing a polymer blend, such as HPC and EC, it is possible to precisely control the drug release rate of an extremely water-soluble drug, such as oxprenolol hydrochloride (130). The water-soluble HPC swells in water and is trapped in the water-insoluble EC so that the drug release is controlled. In another study, the granulation of highly soluble drugs such as dimenhydrinate was performed by the solvent evaporation technique, in which preheated ethanol was gradually added to a homogenous mixture of the drug and EC to dissolve the blend while continuously heating the mixture on a hot plate and slowly evaporating the solvent, followed by drying the mixture in an oven (128). Coprecipitates of different freely soluble drugs with Eudragit RS or RL were prepared by drying a mixed solution of polymer and drug in ethanol and/or methanol (129,131) through the solvent method. The melting method has been applied with waxy carriers such as Compritol 888 ATO (74) on the freely water-soluble drug sodium ferulate, in which the carrier is melted in a water bath at 75°C and the drug is added with continuous stirring to achieve a homogeneous dispersion. The reduction in the drug release from those CR-SDs is due to the hydrophobic nature of the matrix in which the drug is dispersed at the molecular level, whereby the diffusion of the drug is reduced. Additionally, the use of only hydrophilic polymers has also been applied to some CR-SDs to control the release of highly soluble drugs. A strategy of CR-SDs exploiting HPMC K100M is effective in adequately modulating the release rate of metformin.

The CR effects vary not only with the amount of the polymer but also with the SD preparation technique. SDs prepared by solvent evaporation using methocel K100M can prolong the release of metformin for 10 h at 80% concentration and by the cogrinding method at 83% concentration of the polymer (132).

However, to modify the SD characteristics of poorly water-soluble drugs to CR, both hydrophilic polymers and water-insoluble or slower-dissolving carriers can be used. A challenge is that most polymeric excipients are readily water-soluble but may have limited capability to provide the desired amorphous SD, whereas water-insoluble carriers may produce the desired amorphous SD but tend to exhibit poor drug release. The key is probably the addition of an excipient to the composition that would promote dissolution, such as disintegrants, water-soluble polymers, pH modifiers, plasticizers, surfactants, and binders. A dissolution promoter can be used to produce CR formulations and further enhance the overall solubility of the poorly soluble drug. Regarding SD types, conventional SDs or pH-modified SDs can be present in such CR-SDs. The combination of CR and SD is an attractive approach, as supersaturation of the drugs can be achieved by applying SD and retained oral devices in the stomach for a prolonged period to ensure slow delivery of drug above its absorption site, which provides increased and more reproducible drug bioavailability (133). Because the release of drug from such a diffusion-controlled system is driven by the gradient of the drug concentration resulting from the penetration of water, the risk of drug recrystallization should be considered to ensure drug supersaturation. For this reason, how to maintain the supersaturation level of drug for an extended time to prevent recrystallization during drug release from dosage form is a critical question. Strategies to avoid recrystallization thus play a major role in the preparation of the systems because the molecular mobility of the amorphous systems depends not only on the composition but also on the manufacturing process (16). In addition to drug properties, polymers can be selected to increase the T_g of the miscible mixture to reduce the molecular mobility or to interact specifically with functional groups of the drugs via molecular miscibility with the drug (134). Additionally, in a study to investigate the effect of polymer type on the dissolution profile of amorphous SDs containing felodipine, Konno *et al.* determined the ability of three different polymers, PVP, HPMC and hydroxypropylmethylcellulose acetate succinate, to stabilize amorphous felodipine against crystallization by reducing the nucleation rate (135). They speculated that these polymers affect nucleation kinetics by increasing their kinetic barrier to nucleation in proportion to the polymer concentration and independently of the polymer physiochemical properties. SDs in which self-emulsifying carriers are applied should also be considered a strategy to overcome drug recrystallization.

Generally, to prepare CR-SDs, the solvent and melting methods are the two most commonly used, although they may be improved or replaced in the future (16). In a study on CR dosage forms of naproxen, Iqbal *et al.* compared systems that had the SD structure prepared by the solvent method with the systems prepared by wet granulation using EC as the rate-controlling polymer (43). Their results show that both methods are useful in developing CR drug profiles. A cumulative 88% of naproxen is released from the SD formulation, compared with 84% from the wet-granulation formulation. However, SD requires lower amounts of polymer (4%) than wet granulation (6%) to produce a similar release profile. SD is more efficient in preparing controlled-release tablets using EC as the rate-controlling polymer, which may be due to more efficient drug trapping in the tablet matrix. The solvent method could be sub-categorized into the dissolving method and the suspending method for the SDs of indomethacin (136), with both the water-insoluble EC and water-soluble HPMC (1:1) as matrices for both the extended-release and the SD properties. The drug dissolution behavior depends on the structures of EC–HPMC matrices, which are governed by the preparation method. In the suspending method, ethanol is used to dissolve the drug first, followed by EC, and it is finally suspended in HPMC to prepare model SDs; in the dissolving method, a mixed solution of ethanol and methylene chloride (1:1, *v*/*v*) is used to dissolve all three components of SDs (this method repeats the steps in the suspending method to obtain the suspended solution containing HPMC, and methylene chloride is added last to dissolve HPMC). Water-soluble polymers are a key factor in the mechanism of drug release from such SDs prepared with both water-insoluble and water-soluble polymers, as the water-insoluble polymer retains its three-dimensional structure during the dissolution, whereas the water-soluble polymer can gel in the matrices or be dissolved and diffuse quickly into the dissolution medium. The preparation method therefore influences the SD internal structure where HPMC is located, thereby governing the mechanism of drug release. Specifically, the SD containing finely and uniformly dispersed HPMC in its internal structure in the dissolving method exhibits drug release following the diffusion mechanism, whereas SD containing a mass of HPMC with a diameter in the tens of micrometers in its internal structure exhibits a drug release mechanism divided into two phases under sink conditions: release together with HPMC erosion and diffusion from insoluble EC matrices for the suspending method. The latter method has been applied for a novel disintegration-controlled matrix tablet with SD granules of nilvadipine, a poorly water-soluble drug (3,5). A mixture of ethanol and

dichloromethane is used to dissolve the drug and HPMC, and then L-HPC and/or lactose are suspended in the solution, followed by solvent evaporation by a vacuum dryer at 40°C and screening to obtain SD granules. The CR matrix tablets are then compressed after blending magnesium stearate with the melts of SD granules with hydrogenated soybean oil which was previously cooled to room temperature and sieved. The matrix tablet consisting of wax and SD granules containing a disintegrant controls the drug release by its disintegration. The wax limits the penetration of water to the inside of the tablet while the disintegrant swells with the penetrated water, and then the granules are separated from the tablet to release drug. A constant rate of tablet disintegration can be achieved by repeating the processes of water penetration and swelling/separation of SD granules. The novel matrix is a promising CR system, for which the SD technique can be applied to improve the solubility and to sustain the absorption of poorly water-soluble drugs, which has been demonstrated through *in vivo* evaluation.

Optimized Methods

Use of Solvent Quantity as Minimum as Possible

Because the amount of organic solvent is recommend to be as low as possible, other methods have also been introduced, such as the kneading method and cogrinding method. Organic solvent is used in sufficient amounts to completely or partially dissolve poorly water-soluble drugs. In the kneading method, the drug and polymer are triturated using a small volume of solvent (the minimum amount of organic solvent possible) to obtain a thick paste, which is kneaded for a determined time and then dried in an oven if temperature does not affect the system's characteristics. In the cogrinding method, the drug is triturated with a minimum quantity of the solvent in a glass mortar until it is dissolved. The carrier is then added, and the suspension is triturated rapidly at room temperature until the solvent is evaporated. The controlled drug release can be attributed to the amount of polymer, which induces a longer diffusional path and higher viscosity, thus releasing the drug over a longer time at a higher amount. It can also be attributed to the low permeability of the polymer, which poses a significant hindrance to fluid penetration and passive drug diffusion (137). However, there has been a tendency to restrict the use of organic solvents in recent years.

Solvent-Free Systems

Hot-Melt Extrusion. The hot-melt extrusion has become accepted in the pharmaceutical industry as the new alternative because amorphous SDs in various formulations can be obtained to achieve the desired drug-release profiles. The benefits of using hot-melt extrusion over traditional processing techniques include fewer unit operations, better content uniformity, an anhydrous process, a dispersion mechanism for poorly soluble drugs, a low-energy alternative to high-shear granulation, and reduced processing time compared with conventional wet granulation (138). In particular, the melt extrusion method has been used for various purposes in the pharmaceutical industry, such as improving the dissolution rate and bioavailability of the drug by forming an SD or solid solution, controlling or modifying the release of the drug, and masking the bitter taste of an active drug (139). Several researchers have suggested that diffusion CR dosage forms prepared by hot-melt extrusion have slower drug release rates than those prepared by traditional methods due to lower porosity and higher tortuosity (140) because polymeric materials are softened or molten during the process and subjected to intense mixing, resulting in the generation of high pressures (141). PVP, PVP-VA 64, EC, HPMC and PEO are frequently used polymers in the hot-melt extrusion process. Hot-melt extrusion is the process in which a powder blend of drug and carrier is transferred by a rotating screw through a heated barrel of an extruder and then the melt is pressed through a die to obtain a product of uniform shape (142). A critical amount of force must be applied for dispersing and mixing of the powder blend, breaking the aggregates of the minor drug particles. The single screw extrusion, however, does not provide the high mixing capability. Hence, a twin-screw machine with its corotating or counter-rotating screws is the preferred approach for the production of pharmaceutical formulations. Ozawa *et al.* (143) developed the twin-screw extruder method for the SD preparation of water-insoluble and soluble drugs (ethenzamide and theophylline, respectively), which made it possible to control both kneading and heating at the same time under the fusion point of each drug, using Carbopol as the carrier. It is important to not only knead under high pressure, but also to select the optimal operation temperature to bring these drugs into a semi-fusion state. Drug was mixed with the carrier using a mixer for a determined time, and it was then treated with the twin-screw extruder at a determined screw rotation rate, powder supply rate, water supply rate and barrel temperature. Then, the treated mixtures were dried using a dryer, pulverized, dried again and sieved. Their results show a significantly increased solubility of ethenzamide, but a decreased solubility of theophylline. In fact, this method was previously investigated by Nakamichi (144), Miyagawa (67), Sato (145) and co-workers in 1996 and 1997. Nakamichi studied hydroxypropylmethylcellulose phthalate SD containing a poorly water-soluble drug, nifedipine, and noted many advantages to this method, including no required organic

solvents, production at a lower temperature than the melting point of the drug, the softening temperature of the polymer used and the capability of employing various combinations of formulations. Meanwhile, Miyagawa and Sato studied the CR and mechanism of diclofenac release through wax matrix granules composed of carnauba wax, the model drug, and other rate controlling agents. The authors emphasized the advantages of using a twin-screw extruder for wax matrix tablets, such as low temperatures, high kneading and dispersing ability, and low residence time of the material in the extruder. Nakamichi *et al.* published another report a few years later in which the roles of the kneading paddle, screw revolution speed and water content in the preparation of SDs using a twin-screw extruder were found to affect on the dissolution profile of the drug supersaturation (146). In summary, this new pharmaceutical process suggests a useful approach from an ecological standpoint to produce SDs efficiently without drug degradation.

MeltDose. However, it seems that this technology has some disadvantages. The authors of the proprietary technology MeltDose® described some drawbacks of the hot-melt extrusion method, such as up-scaling problems, chemical instability and the use of non-conventional pharmaceutical equipment. MeltDose is suggested to be a one-step industrial process for manufacturing SDs in which the drug is incorporated in a meltable vehicle and the mixture is subsequently sprayed on a particulate carrier such as lactose by fluid bed equipment. Granule particle size is controlled by the product temperature and by optimization of the feed rate and product temperature. The property of granules makes it applicable for direct tabletting without additional processing steps, except for blending with a lubricant. Moreover, the technology is purported to be easily scaled up to manufacturing scale. The technology may be combined with a series of standard formulation techniques used for controlled-release formulations, such as enteric coating, extended release or slow release. MeltDose® has proven to be an effective technology for producing SDs of a number of poorly soluble drugs because it eliminates the drawbacks limiting the use of the SD formulations in drug development. The process may be carried out in a controlled atmosphere (nitrogen) to avoid the degradation of drugs or polymers that might undergo oxidation (147).

Quasi-Emulsion Solvent Diffusion Method. Additionally, the novel quasi-emulsion solvent diffusion method developed by Kawashima *et al.* to prepare the CR microspheres of ibuprofen with acrylic polymers (148) has been applied to prepare CR microspheres containing SD structure. Currently, this technique is used more frequently for the SD preparation of water-insoluble drugs to simplify the manufacturing process and has high potential for improving drug bioavailability. The preparation of the microspheres and the solvent deposition system are combined into a single step. In fact, this is the spherical crystallization technique with the initial stage focusing on improving the powder's flowability and compressibility for direct tabletting, after which polymers are introduced into this system to prepare microspheres, microcapsules, microballoons or biodegradable nanospheres, in which the crystals of drug and polymers are coprecipitated and directly agglomerated into spherical forms according to the polymer properties (149). This method employs three solvents: 1) a good solvent that dissolves the drug, 2) a poor solvent in which the drug is insoluble, 3) a bridging liquid as the solvent that dissolves the drug and is immiscible with the poor solvent and miscible with the good solvent. When the bridging liquid and good solvent containing the drug are poured into the poor solvent under agitation, quasi-emulsion droplets of the bridging liquid or good solvent form in the poor solvent and induce crystallization of the drug, followed by agglomeration (150,151). Using two types of polymers, solid-dispersing (Aerosil) and sustained-release (Eudragit RS), Cui and coworkers prepared sustained-release nitrendipine microspheres that had SD structure (149), improving the bioavailability of nitrendipine. The CR polymer is employed to bind the inert solid-dispersing carrier into microspheres and control the drug release rate. A typical process using this technique could be presented as follows. Drug and CR polymers are dissolved in a mixture of organic solvent (good solvent and bridging liquid). Then, dispersing agent is suspended uniformly in the drug-polymer solution under vigorous agitation. A plasticizer can be added at this stage if necessary. The resultant suspension is then poured into the aqueous phase (distilled water containing sodium dodecyl sulfate as poor solvent) under agitation and a controlled temperature. The suspension is then finely dispersed into quasi-emulsion droplets immediately under agitation, and the drug and polymers are coprecipitated in the emulsion droplets. After agitating the system for a predetermined time, another amount of poor solvent is added slowly, and agitation is continued to promote the diffusion of the organic solvent from emulsion droplets into the aqueous phase to enhance the solidification of quasi-emulsion droplets until the translucent quasi-emulsion droplets turn into opaque microspheres. The solidified microspheres can be recovered by filtration, washed with water and dried to obtain the final products. The drug dissolution rate from microspheres can be significantly enhanced by increasing the amount of dispersing agents and sustained by adding retarding agents. Therefore, the drug release rate could be modulated by adjusting the combination ratio of dispersing agents to

retarding agents. The method suggests that it could also be used to improve the micromeritic properties of solvent deposition systems with a simple preparation process. Additionally, spraying on sugar beads using a fluidized bed-coating system is another approach, in which a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for tabletting or drug-coated pellets for encapsulation in a single step. The method has been applied for both CR-SDs and immediate-release SDs (IR-SDs) (152,153). The commercialized product under the trade name Sporanox® was successfully developed by this method to enhance the dissolution rate of poorly water-soluble itraconazole (154).

The approach in which the constituents of an IR-SD or CR-SD are prepared separately by first preparing the SD, followed by CR processing, could make two systems using the same process that are independent of each other. Therefore, the advantage of this method is that either IR-SDs or CR-SDs can be obtained, depending on the purpose of the study. Either way, there are a variety of methods to choose from for SD preparation. The further processing for CR function presents an option between a coated film over a matrix core composed of SD and a CR polymer further added to make tablets (direct compression or wet granulation) or fill in the capsule. For instance, the CR polymer can be added immediately after the melted SD is obtained in the melting method, and then the whole system can be cooled to obtain the final CR-SD (14,155). The rate-controlling polymer can also be added after obtaining an SD that has been dried, pulverized and sieved, which are also the steps usually met in the case of the solvent process (156,157). The former process is more advantageous than the latter due to its shorter time and greater simplicity. The final CR tablets bearing SDs can be designed as monolithic osmotic tablets (158). The coating approach is usually employed for some common polymers, such as EC, Eudragit and enteric coating (159,160). Table II shows some typical formulations of CR-SD containing poorly water-soluble drugs

EVALUATION OF THE PHYSICOCHEMICAL PROPERTIES OF CR-SD

Similar to the principles for the preparation of CR-SDs, the characterization of the systems' physicochemical properties is based on both the concepts of SD and CR. Common instrumental analyses used in the SD characterization are also applied in CR-SDs, such as detection of crystallinity through differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transformed infrared spectroscopy (FTIR), or water vapor sorption; the detection of molecular structure through confocal Raman spectroscopy, FTIR, temperature-modulated differential scanning calorimetry (TMDSC); the investigation of drug interactions with other excipients through FTIR, Raman spectroscopy, and nuclear magnetic resonance (NMR); the analysis of physical structure by scanning electron microscopy (SEM) and surface area analysis; the analysis of surface properties by dynamic vapor sorption, inverse gas chromatography, atomic force microscopy, and Raman spectroscopy; and, especially, the determination of amorphous content through polarized light optical microscopy, hot-stage microscopy, humidity-stage microscopy, DSC (MTDSC), ITC, and PXRD.

Additionally, to evaluate the CR properties, depending on the type of dosage form, there are corresponding specialized characterizations, such as water uptake studies, swelling and erosion studies, near-infrared spectroscopy (NIR) imaging, and SEM. The polymer swelling process has been investigated through a variety of techniques, such as weighing the swollen and dry polymer (161,162),

Table II Typical Formulations of Controlled Release Solid Dispersion Containing Poorly Water-Soluble Drugs

Drug	Formulation (weight ratio)	Reference
Nilvadipine	hydrogenated soybean oil/solid dispersion containing {drug/HPMC 2910/low-substituted hydroxypropylcellulose (L-HPC)/lactose} (10/{1/3/4.5/1.5})	(3)
Flurbiprofen	Drug/PEO or HPC	(11)
Nitrendipine	Drug/Eudragit E-100 (3/1); Drug/hydroxypropylmethylcellulose phthalate HP-55 (2/1); Drug/hydroxypropylmethylcellulose acetate succinate AS-H (2/1)	(12)
Aceclofenac	PEO/solid dispersion containing {drug/Gelucire® 44/14/Na_2CO_3/poloxamer 407} (1.6/{3.5/3.5/1.4/5}	(14)
Furosemide	Drug/Eudragit RS or RL (5.5/3)	(60)
Felodipine	Drug/HPMCAS (1/3)	(135)
Indomethacin	Drug/EC/HPMC (1/1/1)	(136)
Nimodipine	Drug/Ethyl vinyl acetate/Eudragit RL 100/Ethyl Acetate	(157)
Dipyridamole	Drug/Fumaric acid/Methocel K100LV (1/2/3)	(152)
Indomethacin	Drug/mixture of Eudragit RS and RL (3/3/4)	(182)

observing polymer discs between two transparent Plexiglas® discs during the swelling process (163) and observing the swelling process by magnetic resonance imaging (MRI) (164). Several studies have used MRI to provide a quantitative picture of the swollen gel layer around the dry central core (164–167). One important finding from these studies is the determination of the rate-controlling polymer release. Fyfe and Blazek studied HPMC hydrogel formation by measuring the polymer concentration across the gel layer using a phenomenological equation based on NMR spectroscopy data from HPMC–water mixtures (165). Hyde and Gladden used a one-dimensional, slice-selective, T_1-weighted MRI technique to image the penetration of water into PEO *in situ*, providing simultaneous, quantitative measurements of polymer and water concentration profiles, penetrant front motion kinetics and swelling kinetics (166). In another report, Baumgartner and coworkers developed a procedure for calculating polymer concentration profiles during the swelling of hydrophilic matrix tablets using ^{1}H NMR and MRI (168). The water in the hydrogel not only prevents the polymer network from collapsing, preventing the water from flowing away, but also participates in drug release and serves as the medium for their diffusion within the swollen tablet. In general, the state and dynamics of water within hydrogel samples of different polymer concentrations can be studied by ^{1}H NMR. Therefore, based on the fast exchange of water molecules between the bound state on the polymer chains and the free state in the rest of the hydrogel water, the amount of bound water per polymer repeating unit can be determined. Moreover, through these MRI and NMR techniques, drug release behaviors can be investigated together during the swelling process (169,170).

For the physical characterization of tablets, other parameters are usually evaluated, such as hardness, friability, weight variation, and content uniformity. Other important characterizations that must be carried out in every design of dosage form are drug content and dissolution. To determine drug content, UV spectrophotometry or high-performance liquid chromatography (HPLC) analysis is commonly used. Dissolution analysis usually involves a selection between United States Pharmacopoeia (USP) apparatus 1 (basket) and 2 (paddle). However, the USP apparatus 3 (Bio-Dis), added in 1991 and based on the recognition of the need to establish *in vitro* and *in vivo* correlation, is another approach to test drug release by extended-release products. The advantages of mimicking the changes in physiochemical conditions and the mechanical forces experienced by products in the GI tract can be seen in USP apparatus 3 (171). To characterize the release kinetics to determine the mechanism of drug release, the dissolution data can be fitted to a release equation. For example, the dissolution data of hydrophilic matrices of each batch can be evaluated through different kinetics release equations, such as 1) zero-order: $Q = K_0 t$; 2) Higuchi's square root at time: $Q = K_H t^{1/2}$; and 3) Korsmeyer and Peppas: $M_t/M_\infty = K_M t^n$, where Q is the amount of drug released at time t, M_t/M_∞ is the fraction of drug released at time t, K_0 is the zero-order release rate constant, K_H is Higuchi's square root of time kinetics drug release constant, K_M is a constant incorporating geometric and structural characteristics of tablets, and n is the diffusion exponent indicative of the release mechanism. In the case of tablets of cylindrical shape, a value of $n<0.45$ indicates Fickian or Case I release, $0.45<n<0.89$ non-Fickian or anomalous release, $n=0.89$ Case II release, and $n>0.89$ Super Case II release (172). Finally, a complete research program cannot lack a stability evaluation that is performed through humidity studies, isothermal calorimetry, DSC (T_g, temperature recrystallization), dynamic vapor sorption, and saturated solubility studies. Those characterizations are easily met in a typical CR-SD. Additionally, for the systems containing pH modifiers, there are other specific characterizations, such as the determination of pH modifier release, pH_M. To quantify pH modifier release, samples are withdrawn from the dissolution medium at the same time as for drug analysis and then analyzed. HPLC or UV spectroscopy has been used to determine the release of acidifiers or organic pH modifiers (173–176). However, inorganic or ionizable pH modifiers have been assayed indirectly by potentiometry (applicable to limited ions and requiring longer analysis time), atomic absorption spectroscopy (AAS), atomic emission spectroscopy (AES) and inductively coupled plasma (ICP) spectrometry (which is applicable to a wide variety of elements and reduces analysis time). The results of these quantitative analyses reflect the capability of maintaining a sufficient amount of pH modifier to modulate the pH_M of solid dosage forms. In attempts to measure the pH_M of a solid dosage form, several techniques have been proposed to determine the pH on the surface of or inside a solid dosage form or both. A modified dissolution apparatus and constant-surface area discs, which have been incorporated with a micro-pH probe to measure the pH at the surface of the dissolving compact (177), have been used. Other approaches include pH measurement of a slurry (178); the indicator dye-sorption method in the measurement of solid surface pH (179); electron paramagnetic resonance imaging (EPRI), which was originally used to evaluate pH_M inside pH-controlled matrix tablets containing pH-sensitive spin labels (180); quantification of spatial distribution pH_M by confocal laser scanning microscopy (CLSM) (181); and direct pH_M determination, which was developed by Siepe *et al.* (176) and is easily applicable to a dry solid and has been applied in recent studies (32,33). Additionally, for polymers with properties like HPMC, by determining the cloud points, it

is possible to predict if a matrix could show burst release in a given electrolyte solution. A reduction in cloud points is an indication of decreased solubility of the polymer, so this can be used to characterize the decreased ability of HPMC to absorb water by exposing it to fluids to form a protection gel around the surface of the tablet (83).

To further describe the physicochemical characteristics of CR-SDs, a few specific studies are summarized below. In the two decades since Oth and Moës investigated the sustained-release SD of indomethacin with Eudragit RS and RL, only a few of analyses have characterized SD properties (182). At most, 20% or 30% of drug could be dispersed at the amorphous state in Eudragit RS or Eudragit RL, respectively, as demonstrated by PXRD. The release profiles of the drug can be fitted to the square root of time in the Higuchi model, with the slower release rates from Eudragit RS than Eudragit RL. Moreover, by determining the particle size distribution of the coevaporated SD, the release rate of drug was found to decrease as the size was increased from 100 to 630 μm. Interactions between the drug and Eudragit RL also investigated in an adsorption study followed a type 1 Langmuir isotherm. The tabletting properties of coevaporates were studied and showed no influence of tabletting forces on the Higuchi release rate constant. Today, there are additional techniques to employ in characterizing CR-SDs. Metoprolol tartrate, a hydrophilic agent used in cardiovascular and heart failure, has been introduced in the CR-SDs using different ratios of Eudragit RLPO and RSPO (183). PXRD, DSC, IR, and microscopic observations are performed to evaluate the physical characteristics of SDs. The disappearance of the specific characteristic peaks of drugs confirms the amorphous state change of drugs in SDs through DSC and PXRD. The absence of any other new peaks in the FTIR spectra indicates that the drug is not undergoing any chemical change during preparation. The particle size distribution of the dispersion is also an important factor in controlling the drug release rate. The optimized CR patterns follow zero-order and Higuchi kinetics, depending on the optimal ratio of Eudragit RL/RS and the preparation method (solvent method or melting method). Moreover, FTIR and DSC analyses in a study of CR-SDs of metformin revealed the difference between two preparation methods. In FTIR, weak hydrogen bonding was shown by a shift and reduced intensity of the characteristic band of drug at 3,369 cm^{-1} and 3,294 cm^{-1} in the case of the solvent evaporation method, indicating it was less likely to be stronger than SD by cogrinding (132). In DSC, slight reductions of fusion enthalpy and the melting temperature of drug were particularly observed in the cogrinding SD, which could be ascribed to some drug–polymer interaction occurring during sample preparation. For a slightly water-soluble drug, Ozeki *et al.* (11) investigated the application of SD methods to the CR of flurbiprofen with HPC or PEO. The dissolution property of the polymer strongly influences drug release. In FTIR spectra, the new band observed at 1,736 cm^{-1} and the peak height ratio (the peak height at 1,736 cm^{-1}1/the sum of that at 1,703 cm^{-1} and that at 1,736 cm^{-1}) were attributed to hydrogen bonding between the drug and PEO in the PEO-based system. A linear relationship between the peak height ratio and the drug release rate was observed, probably due to an increased ratio of hydrogen bonding of drug to the increased proportion of PEO in the SD. Glipizide, a poorly water-soluble drug, was investigated in a CR-SD system composed of HPC (184). The release rate of glipizide is markedly enhanced by this system, especially with a lower HPC molecular weight. The controlled drug release is affected by SD granule size, the molecular weight of polymer and the pH of the medium. Drug release mechanisms from a multi-unit erosion matrix system for CR were characterized through FT-IR, SEM, DSC, PXRD and HSM. The melting peak in SD shifted slightly to a lower temperature compared to the pure drug, indicating a change of drug crystallinity to amorphous form by DSC, which was also shown by PXRD and confirmed by SEM. The FTIR study indicated the presence of hydrogen bonding in SD. HSM has demonstrated the ability of melted HPC to dissolve the crystal of glipizide at increasing temperatures. Later, pellets containing optimized SD of glipizide–HPC were prepared to optimize the drug CR. For SDs employed by the twin-screw extruder method, Ozawa *et al.* prepared the SDs of water-insoluble and soluble drugs (ethenzamide and theophylline) simultaneously using Carbopol (143). In this research, PXRD and DSC evaluation showed that when both mixtures are treated with a twin-screw extruder, SDs can be formed with the amorphous state of both drugs. In the FTIR study, ethenzamide in the SD showed a new peak at 3,455 cm^{-1}, which was thought to be due to interactions between the primary amide of ethenzamide and the polymer during SD formation, resulting in various associations, such as hydrogen bonding between the $–NH_2$ group of ethenzamide and –COOH group of the polymer. Similarly, SD of theophylline showed a shift of the N–H deformation vibration to 1,625 cm^{-1}, suggesting that the formation of SDs of theophylline and Carbopol is due to interactions of the two components via hydrogen bonding between the N–H of theophylline and –COOH of Carbopol. Meanwhile, in another study utilizing this technique by Nakamichi *et al.* (146), other parameters were analyzed. The authors found that the kneading paddle elements of a twin-screw extruder play a key role in transforming the crystalline drug to an amorphous form during SD preparation, which was also determined through DSC and PXRD. Operating conditions such as screw

revolution speed and the amount of water added are important parameters in the preparation of SDs. It is important to set the screw revolution speed to maintain the residence time of the materials required in the extruder in order to obtain ideal dispersion of the drug in the polymer matrix. A capillary rheometer is therefore useful to predetermine the operating conditions, such as the amount of water added and temperature for the preparation of SDs. For a CR-SD that has a self-emulsifying structure, Nazzal *et al.* developed self-nanoemulsified tablet dosage form of ubiquinone in which a eutectic-based self-nanoemulsified drug delivery system was first prepared, then adsorbed by granular materials and finally compressed into tablets. They investigated the effects of formulation ingredients on the drug release rate and optimized the formulation as well as variables of Carr's flowability index, including compressibility, angle of repose, angle of spatula, uniformity coefficient and cohesion (185). The flowability index value ranged from 77 to 90, reflecting good flow and improved flowability of the CR formulations, compared to the value of 61 for the IR formulation. Due to their unique and strong interaction with lipids, silicates affect both the rate and extent of lipid release from its solid carrier. However, a study of such self-emulsified systems should analyze turbidity, particle size distribution and particle morphology by an imaging method, for instance, transmission electron microscopy (TEM). The turbidimetric evaluation is performed to monitor the growth of emulsification, where a weighed amount of the system is added to a fixed quantity of a suitable medium under continuous stirring on magnetic hot plate at an appropriate temperature, and then the increase in turbidity is measured with a turbidimeter. Additionally, because it specifies the rate and extent of drug release, the droplet size of the emulsion is a crucial factor in self-emulsification performance (186), which is determined by photon correlation spectroscopy (PCS), especially when the emulsion properties do not change upon infinite aqueous dilution (187). However, microscopic techniques should be employed at relatively low dilutions to accurately evaluate droplet size. Utilizing dye solubilization, dilutability by the dispersed phase excess should also be assessed, as well as conductance and charge measurements (188,189). The properties of CR-SDs, including pH modifiers, are typically investigated by those characterizations plus pH_M determination. One study in which the CR-SD was prepared by physically mixing PEO with the previously prepared IR-SD consisting of aceclofenac, Gelucire® 44/14, pH modifier Na_2CO_3 and poloxamer 407 using the hot-melting method (14) analyzed nearly all of the characteristics mentioned above. The CR-SD system was considered to be effective not only for controlling the drug dissolution rate but also for maintaining an efficient amount of alkalizer inside the dosage forms for pH_M modulation. The physicochemical properties of the system were explored by measuring particle size by dynamic light scattering (DLS), zeta potential analysis, TEM, evaluation of pH_M, chemical imaging of the PEO distribution using NIR microscopy, and the drug structural behaviors using DSC, PXRD, and FT-IR. Although the droplet size of both the IR-SDs and CR-SDs gradually decreases as a function of time, there is a large difference in particle size between these two systems: the CR-SDs are larger than the IR-SDs. Interestingly, the particle size of the IR-SDs significantly decreases, whereas the particle size of the CR-SDs is almost unchanged, as the alkalizer (Na_2CO_3) concentration is doubled. Moreover, the zeta potential values are useful in elucidating the controlled drug release mechanism because of the difference between IR and CR formulations. As more alkalizer is added into the formulation, the zeta-potential is decreased slightly but not significantly. The zeta-potential of the CR-SDs with PEO is much higher when the surface charge is positive with respect to the IR-SDs because PEO can form a shell layer covering the original nanoparticles, which leads to decreased exposure of the hydroxyl groups located on the surface of nanoparticles in the CR-SDs and which also indicates that the PEO in CR-SDs can control the drug release. The surface charges become more negative as a function of time when the PEO shell layer gradually disappears. Thus, PEO in CR-SDs retard drug release. TEM images of the CR-SDs also show much larger droplets compared with the IR-SDs. Additionally, the pH_M of each sectioned dosage form is increased in proportion to the increased amount of alkalizer, but the pH_M of the IR-SD without PEO decreases slightly as a function of time. The PEO by itself does not significantly affect the surface or core pH_M within 15 min but efficiently modulates the pH_M of the dosage forms by retarding the release rate of the pH modifier. As the dissolution fluid penetrates into the dosage forms, the PEO swells gradually and can prevent the alkalizer from leaching out, leading to a decrease in the pH_M. NIR imaging also demonstrated the release behaviors of PEO from the dosage forms, as the polymer, drug and other excipients located on the gel layer during water uptake and drug release can be visualized through NIR imaging. The intensity of PEO on the outer edge of samples increases as a function of time, indicating the gradual formation of a PEO gel layer around the dosage form for drug CR, whereas as the PEO gel structure is exposed, it becomes progressively weaker and erodes faster, indicating rapid drug release. For the instrumental analyses such as DSC, PXRD, FTIR, the results show that only the pH modifier plays a key role in enhancing the drug dissolution rate via structural changes and molecular interactions, but PEO has no effect on these properties.

Accordingly, these characterizations are helpful to elucidate the dissolution-modulating mechanism of the systems.

CONCLUSIONS

An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. CR delivery systems obtained considerable attention from pharmaceutical scientists worldwide for maintaining the desired blood levels of drugs, with narrow therapeutic fluctuation ranges, for extended periods of time after a single administration. On the other hand, SD technologies are particularly promising because the *in vivo* absorption rate is concurrently accelerated with an increase in the rate of drug dissolution, making SDs especially useful for improving the *in vivo* bioavailability of poorly water-soluble drugs. Therefore, the combined and synergistic approaches of CR-SDs containing poorly water-soluble drugs have become a valuable technique to achieve optimal drug bioavailability in sufficient quantities at the appropriate sites in a controlled manner, providing the predictability and reproducibility of the drug release kinetics. The current CR-SD techniques provide a good foundation for further investigation of optimal therapeutic delivery systems through a scientific understanding of different polymeric carriers and their drug release-modulating release mechanisms, preparation methods and methods of characterizing their physicochemical properties using diverse instrumental methods.

ACKNOWLEDGMENTS

This work was supported by the Ministry of Education, Science and Technology and by a grant from the Korean Health Technology R&D Project, Ministry for Health and Welfare (A092018).

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