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REVIEW ARTICLE

Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility

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Abstract

The inclusion of certain polymers within solid dispersion or lipid-based formulations can maintain drug supersaturation after dispersion and/or digestion of the vehicle, leading to improvements in bioavailability and variability in exposure. This review presents an overview of the fundamental principles that underpin drug precipitation mechanisms, describes the mechanisms by which precipitation may be inhibited, discusses the methods that can be used to identify polymeric precipitation inhibitors (PPIs), and summarizes current literature evidence of the most effective PPIs. Preliminary data from our laboratory is also presented, which describes the precipitation inhibition behavior of 53 polymeric materials using supersaturated solutions of danazol as a model, poorly water-soluble drug. These studies identify a group of PPIs with superior precipitation inhibition qualities, the majority of which are cellulose-based. These new results in combination with previous published data indicate that PPIs represent an appealing new technology with the potential to improve drug absorption for poorly water-soluble drugs. The molecular determinants of polymer utility, however, remain relatively poorly understood, although the cellulose derivates appear, in general, to provide the most benefit. More detailed studies are therefore required to define the parameters that most effectively predict and quantify the drug–polymer relationships that control precipitation inhibition.

Keywords: Supersaturation, lipid formulation, crystallization, polymer, solid dispersion, danazol, inhibition, metastable, bioavailability

Introduction

The development of effective formulation approaches to facilitate oral absorption of poorly water-soluble drugs is a considerable challenge. Whilst advances have been made in the design of delivery technologies such as solid dispersions, lipid-based formulations, and micro- and nanosuspensions, in many cases formulation development remains empirical and uncertain. As such efforts to develop alternate mechanisms to promote intestinal solubility continue with some pace.

Historically, approaches to enhance the absorption of poorly water-soluble drugs have revolved around efforts to increase apparent equilibrium solubility in the gastrointestinal (GI) tract or to increase the rate of dissolution. In recent years, however, attention has shifted with the realization that increases in intestinal solubilization may only need to be fleeting, especially for highly permeable molecules, and therefore that maintenance of a temporary state of supersaturation (where the concentration of solute within the solution is above the thermodynamic equilibrium solubility) may be sufficient to promote absorption. Indeed, supersaturation as a means to provide higher thermodynamic activity may enhance absorption over and above that of a simple solution.

There are several ways in which a transiently supersaturated state can form in the GI tract *in vivo*, but these might usefully be simplified into two general cases. In both cases, supersaturation is invoked by a rapid change

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to solubility properties. In the first case, supersaturation may occur on gastric emptying of weak bases. Such compounds are more readily ionized in the acidic environment of the stomach and are therefore significantly more soluble in the largely aqueous gastric content. On emptying into the small intestine, the pH is raised, and the degree of ionization and equilibrium solubility typically are reduced. In the absence of immediate precipitation, a state of supersaturation is therefore formed relative to the equilibrium solubility of the drug in the intestinal fluids. In the second case, supersaturation can result from the loss of solubilization capacity of a formulation as it is diluted, dispersed, or digested in the GI tract. The simplest exemplar of this scenario is the dilution of a formulation comprising drug in a water-miscible or water-soluble "co-solvent" such as PEG 400. In such circumstances, the drug is initially in solution in the formulation, but as the formulation dissolves, supersaturation (or precipitation) ensues (assuming the absence of a notable impact of the co-solvent on the overall solubilization capacity of the intestinal fluids). A similar situation may eventuate on dissolution of solid dispersion formulations (SDF) containing high-energy crystal forms, and on dispersion or digestion of certain lipid-based formulations where the dispersed or digested components have reduced solubilization capacity.

Whether transient supersaturation is beneficial or catastrophic largely depends on the speed of drug precipitation from the supersaturated state. Where precipitation is slowed for long enough for appreciable drug absorption to occur, considerable benefits can accrue. As such the identification of excipients that slow the rate of precipitation from supersaturated solutions has become of increasing interest. The generation of a supersaturated state and subsequent inhibition of precipitation have been referred to as a "spring and parachute" approach (Guzmán et al., 2007), see Figure 1.

Until recently, this has been an area that has been relatively poorly explored after oral administration, and the majority of historical literature describes the use of excipients to stabilize supersaturated solutions in transdermal formulations (Kondo and Sugimoto, 1987). Interest in the use of polymers as a basis for the formulation of solid dispersions, however, has rekindled interest in the potential for excipients, and in particular polymers, as precipitation inhibitors in oral formulations.

Polymers are an important component of solid dispersions and are utilized to stabilize high-energy (and therefore more soluble) crystal forms, such as amorphous state, within the formulation and to alter the dissolution/disintegration properties (Vasconcelos et al., 2007). It has become apparent, however, that the presence of an appropriate polymer can also assist with maintaining drug supersaturation levels after dispersion of the vehicle, thereby improving bioavailability and decreasing variability. This has been the focus of numerous studies to find a polymer that maintains the drug in an amorphous state and also maintains supersaturation after dissolution

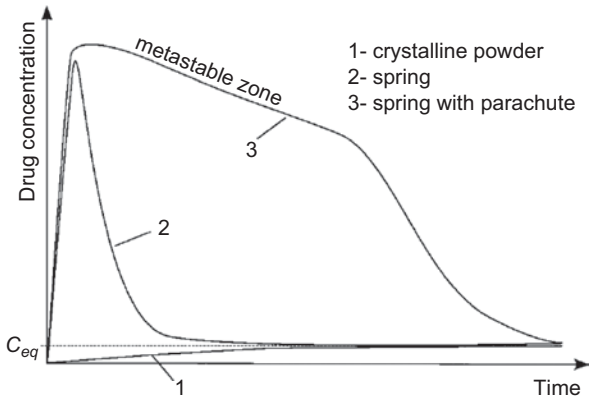


Figure 1. Representation of the spring and parachute approach for supersaturation drug delivery systems, aqueous drug concentration versus time profiles. Profile 1: dissolution of crystalline drug, profile 2: dissolution of amorphous solid dispersion or dispersion of lipid formulation (the spring) in the absence of precipitation inhibitor(s), and profile 3: dissolution of amorphous solid dispersion or dispersion of lipid formulation in the presence of precipitation inhibitor(s) (the parachute). C_{eq} represents drug equilibrium aqueous phase solubility. Reproduced from Brouwers et al. (2009).

of the tablet (Chutimaworapan et al., 2000; Crowley and Zografi, 2003; Gupta et al., 2005; Vandecruys et al., 2007; DiNunzio et al., 2008; Miller et al., 2008).

The principle of maintaining supersaturation within the dispersed aqueous phase formed after formulation dispersion (or disintegration and dissolution in the case of a solid dispersion) using polymeric precipitation inhibitors (PPIs) is now increasingly being applied to lipid formulations (Erlich et al., 1999; Gao et al., 2003, 2004, 2009; Gao and Morozowich, 2006).

Against a backdrop of this recent upsurge in interest in PPIs, we now review the available literature describing the application of PPIs to both solid dispersions and lipid formulations (since the immediate result of both systems is the same, i.e. dispersion of drug and polymer into the aqueous phase). This review includes an overview of the fundamental principles dictating precipitation potential and the possible mechanisms of inhibition, a description of the techniques available for identifying PPIs and review of the polymers that have been identified to date to exert these effects.

Additionally, we present results from recent work from our laboratories, which has examined the precipitation inhibition properties of a series of 53 PPIs chosen from 22 different polymer classes using supersaturated solutions of danazol as a model poorly water-soluble drug. These data are included in the current review in order to expand the relatively limited scope of the existing data within the literature.

Examples of applications of PPIs in the GI tract

PPIs have broad potential application in the inhibition of drug precipitation in the GI tract. In a later section

entitled "Interactions between polymers and drugs," we present a comprehensive review of the available literature describing polymeric precipitation inhibition and include data extracted from both fundamental studies conducted entirely *in vitro* through to applied studies, where *in vitro* and correlative *in vivo* data are presented. By way of introduction, however, two representative examples are described below, which give an indication of the potential utility of these systems *in vivo*, and which also illustrate the two most common applications described to this point: prevention of drug precipitation (1) after dissolution of SDF and (2) after dispersion of lipid-based formulations.

PPIs and solid dispersions

Yamashita et al. (2003) reported one of the first studies to explore the impact of polymers included in traditional SDF on drug precipitation, from the transiently supersaturated state that was formed after dissolution. This study examined a series of SDF of tacrolimus, a poorly water-soluble (1–2 μg/mL) immunosuppressant. *In vitro* evaluation explored SDF incorporating polyethylene glycol (PEG 6000), polyvinylpyrrolidone (PVP), or hydroxypropylmethyl cellulose (HPMC). As shown in Figure 2, the supersaturation concentration for all of the SDFs were 25 times higher (~50 μg/mL) than the equilibrium solubility, showing how a dispersion of an amorphous drug within a solid matrix can significantly increase the supersaturation concentration. The concentration of tacrolimus in solution after 24 h fell to 6 μg/mL for the PEG 6000 SDF and 30 μg/mL for the PVP SDF. In contrast, the SDF with HPMC maintained the high concentration of tacrolimus over the entire 24 h period, suggesting to the authors that the HPMC prevented the drug from recrystallizing. The bioavailability of tacrolimus was then compared after oral administration of the HPMC SDF and crystalline tacrolimus to male beagle dogs (Figure 3). The crystalline drug produced blood levels with a C_{max} of 0.4 ng/mL and $AUC_{0-8\,h}$ of 1.1 ng h/mL, whereas the HPMC SDF led to a C_{max} of 4.0 ng/mL and $AUC_{0-8\,h}$ of 10.9 ng h/mL. The presence of the PPI HPMC therefore led to a 10-fold increase in the C_{max} and AUC when compared with administration of the crystalline powder.

PPIs and lipid formulations

A similar approach to precipitation enhancement for lipid-based formulations is well-exemplified by the studies from Gao et al. (2003) who explored the application of PPI to a series of self-emulsifying drug delivery systems (SEDDS) of paclitaxel. On *in vitro* dispersion, and in the absence of HPMC, the SEDDS formulation led to the generation of a paclitaxel concentration of 0.12 mg/mL after 10 min, which then decreased further to 0.03 mg/mL after 30 min (Figure 4). This rapid decrease in the aqueous concentration was suggestive of precipitation, and drug crystals were observed within the simulated gastric fluid (SGF). When 5% w/w HPMC was included in the SEDDS

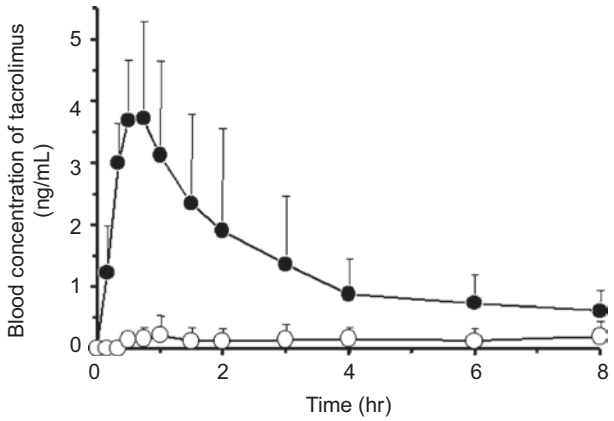


Figure 3. Blood concentration of tacrolimus after oral administration of (filled circle) solid dispersion formulation with hydroxypropylmethyl cellulose and (open circle) crystalline powder. Reproduced from Yamashita et al. (2003).

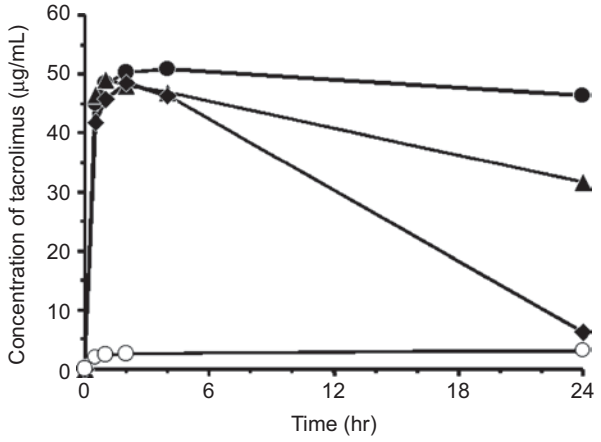


Figure 2. Dissolution profiles of tacrolimus from solid dispersion formulations: (filled circle) hydroxypropylmethyl cellulose, (filled triangle) polyvinylpyrrolidone, (filled diamond) polyethylene glycol 6000, and (open circle) crystalline tacrolimus. Reproduced from Yamashita et al. (2003).

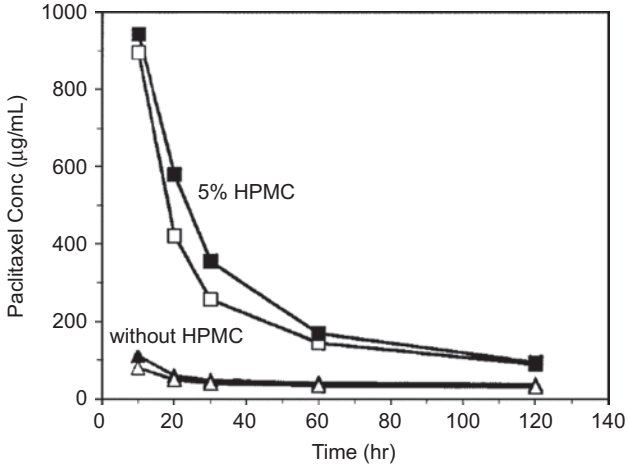


Figure 4. Apparent *in vitro* paclitaxel concentration–time profiles from self-emulsifying drug delivery systems formulations with (filled and open squares) and without (filled and open triangles) hydroxypropylmethyl cellulose. Solid/open symbol pairs are duplicates. Reproduced from Gao et al. (2003).

formulation, after 10 min the concentration was 0.95 mg/mL and fell to ~0.35 mg/mL after 30 min. Indeed, it was not until 2 h after dispersion of the HPMC SEDDS that the paclitaxel concentration fell to the same level as that observed 10 min after dispersion of the polymer-free formulation. The presence of the HPMC therefore assisted in maintaining the supersaturated drug solution *in vitro*.

Subsequent *in vivo* evaluation in male Sprague-Dawley rats compared SEDDS formulations with and without HPMC (Figure 5). The SEDDS formulation resulted in a paclitaxel C_{max} of 13.1 ng/mL and oral bioavailability of 0.9%. In contrast, the SEDDS formulation containing HPMC resulted in a 20-fold increase in C_{max} to 300 ng/mL and 10-fold increase in oral bioavailability to 9.5%. HPMC was therefore highly effective in suppressing precipitation and ultimately led to enhanced oral bioavailability.

These examples provide an introductory "proof-of-concept" to frame the potential utility of PPIs. In light of these potential benefits, the following sections provide a brief overview of the mechanisms of drug precipitation from supersaturated solutions and explore the theoretical background to the use of polymeric material to inhibit this precipitation event.

Precipitation/crystallization

Precipitation is the phase separation of solid material from a solution, melt, or gas phase. The overall mechanism is similar in all of these three phases, but the remainder of this review concentrates on the solution phase. Where the resulting solid phase is arranged in an orderly, repeating three-dimensional pattern, the process is typically referred to as crystallization. Phase separation of noncrystallization (amorphous) material may also occur. The mechanisms that drive phase separation are common, irrespective of whether an amorphous or crystalline solid is produced; the differences lie only in the nature of the packing of the solid material formed. In the absence of specific knowledge of the physical form of the phase-separated material, a more generic description of a "precipitate" (which may include both crystalline and amorphous material) is commonly utilized and this terminology is employed in large part throughout this manuscript.

Much of the available literature describing the initiation of crystallization or precipitation from supersaturated solutions, however, has focused specifically on crystallization and, therefore, in the following section the process of crystal nucleation and growth is described. Nonetheless, an analogous situation could be envisaged for the formation of phase-separated amorphous material.

For crystallization to be initiated and continue, a solution has to be supersaturated with respect to the solute, so that crystallization is thermodynamically favored. Once initiated, the process will continue under kinetic control until supersaturation is lost. The crystallization process is complex and influenced by the environment and physical conditions of the solution, including solution composition, the presence of impurities, nucleation, solution solubility, solution saturation and degree of supersaturation, crystal growth, temperature, and pH, and to date is not fully understood. Three theories (surface energy, diffusion, and adsorption layer) have been developed to explain and model the crystallization process, all of

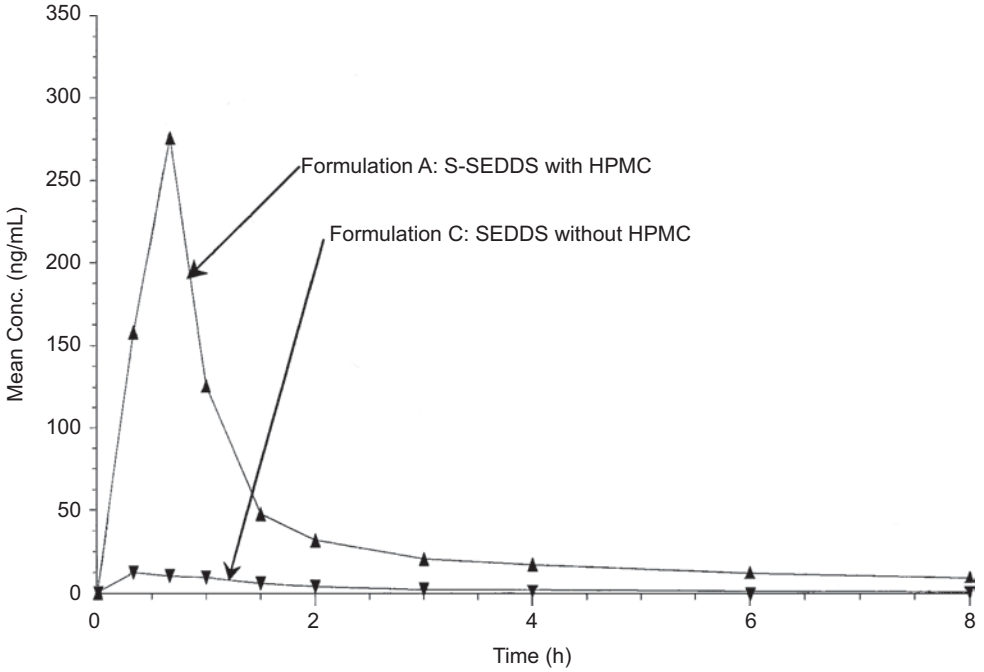


Figure 5. Mean plasma concentration–time profiles of paclitaxel in rates after oral administration of 10 mg/kg paclitaxel using the self-emulsifying drug delivery systems formulations with (filled triangle) and without (filled inverted triangle) hydroxypropylmethyl cellulose. Reproduced with modifications from Gao et al. (2003).

which currently have failings in explaining some of the phenomena observed experimentally (Mullin, 2001).

Surface energy theories are based on the principle that a droplet of a fluid is most stable when the area/surface free energy is at a minimum and that crystal growth is a special case of this. There is little quantitative evidence supporting this theory, the main problem being that it fails to explain the effect of supersaturation and solution agitation on growth rates.

Diffusion theories describe the integration of units into the crystal via diffusional control, where the surface of the crystal is coated in a stagnant film. The diffusion theory fails, however, when the system is agitated, since the size of the diffusion film reduces close to zero, implying very rapid (almost infinite) crystallization rates, a physical impossibility. As a result, diffusion theory has been extended to a two-step process: (1) diffusion of solute from the bulk solution to the crystal surface, followed by (2) rearrangement on the crystal surface prior to integration into the crystal lattice. This two-step kinetic process remains a considerable simplification, with the following processes occurring simultaneously (Mullin, 2001):

1. Bulk diffusion of hydrated solute through the diffusion boundary layer.
2. Bulk diffusion of hydrated solute through the adsorption layer.
3. Surface diffusion of hydrated or dehydrated solute.
4. Partial or total dehydration of solute.
5. Integration of solute into the crystal lattice.
6. Counter-diffusion of released water through the adsorption layer.
7. Counter-diffusion of water through the boundary layer.

Currently, the diffusion theories cannot be reconciled with adsorption layer or dislocation theories, and fail to explain layer growth or faceting of crystals.

The third crystallization theory, the adsorption layer model, is based on thermodynamic reasoning and the concept of an adsorbed layer of solute existing on the crystal face. When a solute molecule arrives at a crystal face, it is not immediately incorporated into the crystal lattice. It becomes loosely adsorbed to the face and has the freedom to diffuse around the surface. Therefore, an equilibrium exists between the adsorbed layer and the bulk phase solute. Growth of the crystal occurs as the solute molecules find a position on the face where the attractive forces are highest, typically a kink in a lattice growth step. The step continues to grow until the face is completely covered; further growth requires the formation of a nucleation point on the two-dimensional crystal surfaces. A failure of the adsorption layer model is that under low supersaturation levels, the surface nucleation model fails to predict the correct crystal face growth rates. This problem is solved by considering the fact that the crystals are not perfect and imperfections occur in the growing crystal lattice. Screw dislocations (crystal dislocation in which crystal planes form a spiral ramp around the dislocation line) are the most important imperfections, eliminating the need for surface nucleation and providing the basis for the face dislocation theory. Once a screw dislocation forms, the crystal face can continue to grow. Since a smooth layer is never formed with a screw dislocation, the growth rate is similar to that if the crystal surface was covered in kinks, which is close to the maximum theoretical growth rate for a given supersaturation level.

The crystallization process is divided into two distinct stages/processes: nucleation and crystal growth. Nucleation and growth occur simultaneously, with the physical conditions dictating the relative contribution of both processes. As such, a polydispersion of particle sizes and ages is present within the system at any one time (Rodríguez-Hornedo and Murphy, 1999). Many compounds can form different crystal structures or polymorphs; however, the polymorph that is formed is not necessarily the most stable, it may simply be kinetically favored (Dunitz and Bernstein, 1995). The rate and mechanism of crystallization is determined by the solute solubility, degree of supersaturation, the rate at which supersaturation is created, diffusivity, temperature, and the reactivity of surfaces toward nucleation.

The basics of the crystallization processes are summarized in the following sections. For a more thorough treatize of crystallization fundamentals see Mullin (2001), for nucleation see Kashchiev and van Rosmalen (2003), and in terms of pharmaceutical systems see Lindfors et al. (2008) and Rodríguez-Hornedo and Murphy (1999).

Nucleation

During nucleation, solute molecules initially gather into two (on the surface of an impurity)- or three (in free solution)-dimensional clusters within the solution. These nuclei reach a stable state by exceeding a critical size. In any solution, there is a fluctuational appearance of nanosized clusters of crystalline phase (Kashchiev and van Rosmalen, 2003) and if the clusters are of insufficient size, then they spontaneously disintegrate. Those that are larger than a critical size continue to grow and move onto the next stage of crystallization, that is, crystal growth. It is at this stage that the molecules arrange themselves in the periodic manner that is the basis for the crystal structure.

Two types of nucleation can occur: homogeneous and heterogeneous. Homogeneous nucleation occurs very rarely, as impurities are almost always present, leading to induction of heterogeneous nucleation. Heterogeneous nucleation involves a surface or interface of different composition (such as an impurity), onto which the solute crystallizes. The presence of impurities decreases the energy barrier for the formation of the nuclei that ultimately grow into crystals (Rodríguez-Hornedo and Murphy, 1999) and therefore the critical cluster size is

significantly smaller than for homogeneous nucleation processes (Kashchiev and van Rosmalen, 2003).

Supersaturation of a solution with respect to solute is insufficient to initiate nucleation; nuclei or seeds are required. Therefore, under suitable conditions nucleation can be delayed almost indefinitely through the formation of a metastable state, even though the crystallization process is thermodynamically favored (Dunitz and Bernstein, 1995). The nucleation step represents an activation energy barrier to the spontaneous formation of a crystalline phase from a supersaturated solution. A disturbance to the metastable state is all that is required to initiate nucleation, such as a mechanical disturbance or the introduction of a seed crystal or impurity. As the degree of supersaturation increases, the likelihood of nucleation rises and the metastable state only exists up to a critical degree of supersaturation, beyond which the labile state undergoes spontaneous crystal formation (Sangwal, 2007).

The period between the generation of supersaturation and initiation of nucleation is the induction period. The length of this period depends on temperature, pressure, the presence of impurities or seeds, and mechanical disturbances. The presence of seeds and increased supersaturation decrease the length of the induction period (Sangwal, 2007). Induction time can be determined optically from the change in the intensity of light transmitted through the supersaturated system (Kashchiev and van Rosmalen, 2003).

Nucleation rates for homogeneous systems can be experimentally controlled by the following parameters: molecular/ionic transport (increased frequency of transport at the crystal nucleus–liquid interface increases nucleation rate), viscosity (increased viscosity decreases the frequency of molecular transport), supersaturation (increased supersaturation increases the nucleation rate), solubility (at constant supersaturation, increasing solubility increases the probability of intermolecular collisions, increasing the nucleation rate), solid–liquid interfacial tension (decreased interfacial tension increases the nucleation rate), and temperature (increased temperature decreases the nucleation rate). Interestingly, at higher solubility, the degree of supersaturation required to induce nucleation decreases (Rodríguez-Hornedo and Murphy, 1999).

Growth

Once a critical sized solute cluster is formed in solution, subsequent growth of the nuclei can occur. It must be remembered, however, that growth does not occur in isolation and nucleation continues, with either process dominating depending on the physical conditions. When crystal growth is dominant, for example, fewer, larger crystals are formed, whereas significant ongoing nucleation leads to the generation of larger numbers of smaller crystals. Growth of the nuclei occurs by attachment of more solute molecules to energetically favored growth sites. A model of a growing crystal face is shown in Figure 6, which is made up of moving steps (B)/layers of unit height containing one or more kinks (C). The face will also contain surface adsorbed units (D) and vacancies (F) in the steps and surfaces (G). The growing crystal will not typically maintain the same geometry during crystal growth and smaller, faster growing faces are rapidly eliminated. Thus, assuming the mechanism of crystal growth is the same on each crystal face, the growth rate of a crystal face is related to the surface energy of the face. Under these circumstances, the faster growing faces have a high surface energy and vanish in the final crystal, while the slower growing faces have low surface energy and persist, dominating the final crystal (Mullin, 2001).

Crystal growth is generally considered to occur in the following four stages (Sangwal, 2007), see Figure 6:

1. Transport of molecules to the growing surface by bulk diffusion and their capture on the crystal face terrace (D).
2. Migration of molecules adsorbed on the terrace to the step (B) by surface diffusion and their capture at the step (E).
3. Migration of molecules adsorbed on the step to the kink site and their integration into the kink/crystal structure (C).
4. Transport of the released heat of the reaction and solvent molecules from the desolvated molecules in the above steps.

Crystal habit and impurities

The macroscale form of a crystal is referred to as the crystal habit and can vary depending on the environment and physical conditions under which the crystal is grown. Importantly, the crystal habit may not resemble the crystal unit cell (the smallest possible representative sample possessing the symmetry of the crystal) and different habits can be generated from the same unit cell. The following can influence the crystal habit formed during crystallization:

1. Rate of crystallization.
2. Degree of agitation.
3. Degree of supersaturation.
4. Presence of impurities.
5. Solvent.

Crystallization is sensitive to the presence of impurities within the solution, both soluble and insoluble. Impurities

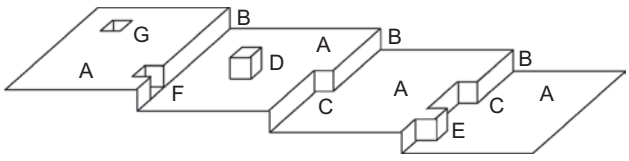


Figure 6. The Kossel (1934) model of a growing crystal face, showing (A) flat surfaces/terrace, (B) steps, (C) kinks, (D) surface adsorbed unit, (E) step absorbed unit, (F) edge vacancy, and (G) surface vacancy.

are considered to be any foreign substance other than the crystallizing molecule (Sangwal, 2007) and can be simple ions, molecules, dust particles, or crystals. The foreign substance can be added on purpose, simply be part of the system or come from an external source. Currently, it is virtually impossible to predict the effect an impurity will have on crystallization (Rodríguez-Hornedo and Murphy, 1999; Mullin, 2001); however, the most potent small molecule inhibitors of crystallization are typically structurally similar to the solute. Some impurities suppress growth entirely, some enhance crystal growth, and others act only on certain faces, modifying the crystal habit. Soluble impurities can change the equilibrium solubility of the solute, change the solution properties, adsorb onto nuclei, alter the characteristics of the adsorption layer at the crystal–solution interface, chemically react with the solute, and even form complexes with the solute (Mullin, 2001).

Impurities may not necessarily affect the equilibrium position of crystallization, and instead, often alter the growth rate under nonequilibrium conditions. This occurs by changing the kinetics of one or more of the four steps of the crystal growth process. These effects can be highly face-specific, increasing, decreasing, or totally suppressing the growth of some faces. This results in a change in the relative growth rate of the crystal faces and hence a change in the crystal habit (Mullin, 2001).

Summary of factors affecting precipitation

In summary, drug precipitation from supersaturated solutions is a complex function of both nucleation and crystal growth, but in general is accelerated by:

1. Increasing degree of supersaturation.
2. Increasing solubility (at constant supersaturation).
3. Presence of impurities to stimulate nucleation.
4. Lower temperature.
5. Low solution viscosity.
6. Decreasing the interfacial tension.

Several approaches have been taken to try to reduce the rate of drug crystallization or precipitation from supersaturated solutions (Brouwers et al., 2009) and here the focus is on the use of PPIs. Prior to a discussion of the specific mechanisms by which polymers may inhibit drug precipitation, a brief description of the typical solution behavior of polymeric materials is provided below.

Polymers in solution

The behavior of polymers in solution is more complex than that of small molecules, a situation largely reflecting the complexities associated with larger molecular size. Nonetheless, solubility behavior is similar dictated by the balance of intermolecular forces between the solvent and solute and the entropy change accompanying solvation. Factors that alter this balance include electrostatic interactions/polarity, ionic strength, van der Waals interactions/hydrophobic effect, hydrogen bonding, temperature, and pressure (Ebewele, 2000; Tonge and Tighe, 2001).

Polymer molecules that are fully solubilized in a good solvent (a theta solvent) exist as random/extended coils. The extended coil conformation is a result of the relative rotational freedom associated with the polymer backbone and the countless number of conformations that the polymeric material can adopt in the absence of significant intramolecular interactions. Consequently, the volume occupied in solution by a solubilized polymer is significantly higher than that of the combined monomeric units. In a poor solvent, intramolecular interactions occur, resulting in the formation of a more contracted random coil confirmation and in the case of a very poor solvent, the polymer will adopt a highly contracted colloidal, globular state, minimizing contact between polymer and solvent.

Two key factors determine the solubilization state of a polymer in solution: the presence of weakly charged functional groups and the presence of additional alkyl components. Ionized weakly acidic or basic functional groups provide a repulsive force between charged groups and promote interaction with aqueous solvents, assisting the formation of an extended coil. In contrast, alkyl components promote the adoption of a minimum interaction volume with respect to solvent in order to minimize disruption to hydrogen bonds between water molecules (the hydrophobic effect). The presence of a sizeable alkyl polymer component, therefore, favors a more contracted globular state by minimizing disorder within the aqueous phase (Tonge and Tighe, 2001).

A complicating factor in the solution behavior of polymers is the kinetics of the processes involved. Due to the large molecular weights (MW) and viscosities of many polymers, the solvation process (Ebewele, 2000) and subsequent aggregation processes can occur over very long time frames, perhaps of the order of months (Bodvik et al., 2010). For this reason, care has to be taken when making conclusions as to whether the phenomena observed is achieved at thermodynamic equilibrium or is kinetic in nature.

For more detailed treatments of polymers in solution, see Jannink and Cloizeaux (1990), and Lapasin and Pricl (1995).

Polymeric precipitation inhibitors

PPIs aim to maintain drug in a supersaturated, thermodynamically unstable state (metastable) over a period of time that is sufficient to allow absorption (for applications in oral drug delivery). As such, their effects are usually kinetic and merely slow the inevitable process of precipitation via inhibition of nucleation or crystal growth. In contrast, effects on the system's thermodynamic (equilibrium) properties are less common. PPIs dominant mode of action is therefore not via co-solvency and they do not typically increase equilibrium drug

solubility. In contrast, surfactants, for example, are also capable of preventing drug precipitation, but typically do so via enhancements in drug solubility stemming from micellar solublization (Dai et al., 2007).

In some circumstances, however, polymers may have an impact on solubility and therefore the prospect for solubility enhancement should at least be addressed when examining the mechanism of precipitation inhibition. For example, increases in precipitation induction times in the presence of polymer are often used to provide an indication of the most effective precipitation inhibitor. While polymer addition may delay precipitation (as indicated by an increase in precipitation induction time), care must be taken when attempting to extrapolate the mechanism of the effect. Where polymer addition does result in an increase in drug solubility, the degree of supersaturation (a prerequisite for precipitation) may be reduced and possibly reduced below the level of saturation. Under these circumstances, precipitation will be inhibited, but via a change to the system thermodynamics (i.e. equilibrium solubility) rather than a change to the kinetics of precipitation.

The polymers that have been reported to enhance drug solubility include PVP that has been found to increase the solubility of acetazolamide and hydrocortisone (Loftsson et al., 1996), felodipine (Karavas et al., 2006), and valdecoxib (Bansal et al., 2007), and HPMC that has been suggested to increase the solubility of acetazolamide and hydrocortisone (Loftsson et al., 1996), and RS-8359 (Usui et al., 1997). One complication when evaluating this data, however, is the potential for solubility measurements to be taken under nonequilibrium conditions for systems that are quite kinetically stable. Thus, where solubility assessments are made by, for example, the addition of a concentrated solution of drug in solvent plus polymer to an aqueous buffer, even measurements taken several days after induction of supersaturation may not reflect true equilibrium solubility. As such, what appears to be a change in drug solubility may in fact be kinetic stabilization of a supersaturated solution. The line between assigning effects to supersaturation stabilization rather than effects on true solubility is therefore blurred. In reality, however, it seems unlikely that significant increases in equilibrium solubility will occur without the addition of quantities of polymer (perhaps >10% w/v in the final aqueous solution) sufficient to significantly change solution properties (i.e. to induce a co-solvent effect). In contrast, PPIs are typically included in formulations at concentrations that are below these levels and the predominant effect is likely to be stabilization of supersaturation. The ability of PPIs to kinetically stabilize the supersaturated state is thought to result from intermolecular interactions between the drug and polymer in solution (e.g. via hydrogen bonding or hydrophobic interactions) and/or the ability of the polymer to sterically hinder the crystallization process (Ziller and Rupprecht, 1988; DiNunzio et al., 2008). For example, in a study of itraconazole supersaturation after dissolution and gastric emptying of a series of polymeric SDF, Miller et al. (2008) concluded that both chemical and physical aspects of the polymer were important determinants of utility. Ziller and Rupprecht (1988) have also demonstrated that interactions between drug functional groups and polymer are necessary, but not exclusive, drivers of crystal inhibition via examination of the impact of a series of structurally related materials on acetaminophen supersaturation. In these studies, crystallization of acetaminophen was not altered, even at high concentrations, by the presence of pyrrolidone, 1-methylpyrrolidone, or piracetam, whereas the structurally similar material PVP successfully inhibited crystal growth. The ability of polymers to present or delay precipitation from the supersaturated solutions that are commonly formed *in situ* after dissolution or dispersion of formulations of poorly water-soluble drugs is therefore complex and to this point, incompletely understood. It is also unclear at this stage whether polymers must be fully solubilized as random coils in order to work most effectively, or whether there is advantage in the presence of polymer in a colloidal state.

It appears, however, that PPIs present can act as crystallization inhibitors at both the nucleation and growth (kinetics and crystal habit) stages and several potential sites of action have been identified (Vandecruys et al., 2007; Liu, 2008):

1. Altering bulk solution properties such as surface tension (where decreasing surface tension moves crystallization from diffusion control to surface nucleation control) and solubility (where increasing solubility reduces supersaturation and the likelihood of nucleation) (Pellett et al., 1997a, b; Machefer et al., 2008).
2. Changing the adsorption layer at the crystal–solution interface, including the properties of the hydrodynamic boundary layer surrounding the crystal, potentially decreasing the rate of diffusion of drug molecules to the crystal nuclei (Raghavan et al., 2001b; Machefer et al., 2008; Gao et al., 2009).
3. Adsorbing to the crystal surface interface, thereby blocking crystal growth by blocking access of the solute molecules to the crystal terrace (Ziller and Rupprecht, 1988; DiNunzio et al., 2008; Machefer et al., 2008; Gao et al., 2009).
4. Adsorbing onto the growth terraces and thereby disrupting the growth of steps across the surface, blocking access of adsorbed molecules to the terrace steps and/or kinks (Gao et al., 2009).
5. Adsorbing into surface imperfections causing rough surfaces to become flat, therefore eliminating growth spots.
6. Altering the surface energy of the crystal face, potentially changing the level of solvation.

In all cases, a chemical or physical interaction between the drug and the polymer underpins precipitation

inhibition. In this regard, the factors that influence the interaction between polymers and drug molecules have been suggested to be:

1. Temperature: binding between drug and polymer is decreased at higher temperatures, due to weakening of intermolecular interactions between the molecules and increased solubility of drug (Plaizier-Vercammen and De Nève, 1981).
2. Molecular weight: higher MW polymers interact more strongly with drug molecules. This effect has been observed for higher MW PVP polymers that are more efficient complexing agents of salicylic acid and its derivatives (Plaizier-Vercammen, 1983), and for higher MW PVP and HPMC that have been shown to more effectively maintain the supersaturation of itraconazole (Miller et al., 2008). This effect can be attributed to either an increase in viscosity or an increase in the number of available functional groups on the polymer chains.
3. Viscosity: increasing the viscosity of the aqueous medium decreases the rate of drug diffusion from bulk solution to the crystal nuclei or surface, inhibiting crystallization, during both nucleation and growth phases.
4. Dielectric constant: decreasing dielectric constant decreases the degree of interaction between polymer and drug molecules (Plaizier-Vercammen, 1983), since the decrease in dielectric constant typically increases drug solubility (Plaizier-Vercammen and De Nève, 1982).
5. Hydrogen bonding: increasing the number of hydrogen bonding sites available may increase the interaction between polymer and drug. For example, itraconazole interacts more strongly with HPMC in solution than with PVP, a result suggested to reflect the presence of hydroxyl groups on HPMC that are capable of hydrogen bonding itraconazole (Miller et al., 2008). Superior inhibition of itraconazole crystallization has also been observed for HPMC and cellulose acetate phthalate (CAP) (both of which have a cellulose backbone) over PVP and polyvinyl acetate phthalate (PVAP) (DiNunzio et al., 2008).

In most cases, polymers will have multiple modes of interaction with drugs and may impact on drug precipitation via several mechanisms, and in some cases these may be counteractive. For example, CAP provides better inhibition of itraconazole crystallization than PVAP, even though PVAP has more hydrogen bonding donor sites available (DiNunzio et al., 2008). In this case, a qualitative comparison of polymer solution viscosities suggests that the higher viscosity CAP solutions when compared with the PVAP were responsible for the improved utility of CAP. In contrast, viscosity was not identified as a significant factor in the inhibition of celecoxib precipitation by hydroxypropyl cellulose (HPC) due to the absence of continued benefit above 4 mg/mL HPC (Guzmán et al., 2007). Prediction of polymer utility *ab-initio* from molecular properties alone therefore remains difficult. Screening mechanism by which the potential for polymers to reduce drug precipitation can be assessed are therefore increasingly important and are described below.

PPI screening techniques

In order to screen potential PPIs, a technique is required that generates a supersaturated aqueous phase in which precipitation can occur, and an analytical method to determine the amount of material that precipitates over time.

Induction of supersaturation

Supersaturation can be created by a variety of techniques including solvent removal, addition of ions that participate in precipitation, dissolution of metastable solid phases, temperature change, pH change, and the addition of solvent that lowers the solubility of the solute (Rodríguez-Hornedo and Murphy, 1999). Of these, three methods have been applied to the study of PPI with poorly water-soluble drugs: co-solvent quenching (addition of solvent), amorphous drug dissolution (high-energy crystal form), and pH change.

The co-solvent quench method is currently the most common. In this method, drug is dissolved into a solvent that has a significantly higher solvent capacity than the aqueous phase. A small aliquot of the solvent (containing high concentrations of dissolved drug) is then dispersed in the aqueous phase to create a supersaturated system. Solvents used include ethanol (Garekani et al., 2000), dimethylformamide (Vandecruys et al., 2007; Brewster et al., 2008), dimethylacetamide (Lindfors et al., 2008; Curatolo et al., 2009), propylene glycol (Raghavan et al., 2001b, 2003), sodium hydroxide solution (Guzmán et al., 2007), and 1,3-dioxolane (Matteucci et al., 2007).

Amorphous drug dissolves more readily than a crystalline form and may be utilized to provide an increase in drug solubility (Brewster et al., 2007). Since the amorphous form is not thermodynamically stable, this increase in solubility is, in effect, a transient supersaturation with respect to the solubility of the stable polymorph. In the case of a SDF containing amorphous drug, it is often assumed that increases in dissolution and ultimately bioavailability reflect the increase in solubility of the amorphous form. However, most solid dispersion employ polymers as the formulation matrix and as such it is often difficult to definitively assign the mechanism of absorption enhancement to improvement in solubility of the amorphous form, the generation of supersaturation, or the subsequent inhibition of precipitation by the polymer.

In the case of drugs that are weak bases, a pH change can be used to create the supersaturated state. The solubility of a weakly basic compound is usually significantly

higher in the ionized form than in the unionized form. Therefore, changing the solution pH from a value lower than the pK_a to higher can be used to generate a supersaturated state. The pH change method has been experimentally applied using a transfer method (continuous addition of SGF to a simulated intestinal fluid, FaSSIF or FeSSIF) (Kostewicz et al., 2004) or by the addition sodium phosphate to acid media (Overhoff et al., 2008).

Method of analysis

In order to determine the extent of drug precipitation, the concentration of the dissolved drug within the aqueous phase or the mass of drug precipitated can be assayed. Measurement of the concentration of drug present in the aqueous phase provides an accurate determination of the extent of precipitation and can be readily determined using, for example, the UV–visible spectrum of the drug (Megrab et al., 1995; Vandecruys et al., 2007) and may include separation via HPLC (Curatolo et al., 2009; Gao et al., 2009). However, due to the inherent delay in sampling and preparation time when using these "off-line" analytical methods, only a relatively low time resolution is possible; 60 and 180 min by Curatolo et al. (2009); 5, 30, 60, and 120 min by Vandecruys et al. (2007); and 30, 60, 120, and 180 min by Gao et al. (2009). Precipitation within the aqueous sample taken from the dispersion will also continue to occur until it is halted by mixing with an organic solvent. This introduces a degree of uncertainty to the actual time points.

Poor time resolution can result in the loss of a significant amount of detail in the precipitation process. An alternative method is to monitor the amount of drug that has precipitated *in situ* and this is possible using turbidity measurements (method described in detail in section titled "Turbidity measurement"). In this case, a nephelometer measures the forward light scattering of the sample and provides a measure of the degree of obscuration of the scattering signal and therefore the number of particles in the sample. Using this method, it is possible to analyze a large number of samples simultaneously, using a plate reader, with much improved time resolution. This technique does not provide an absolute measurement of precipitated drug, but can be used in conjunction with aqueous concentration determination to allow a direct conversion at specified time points.

Interactions between polymers and drugs

Tables 1 and 2 document examples of known interactions between small molecules and (1) a miscellaneous group of synthetic polymers (Table 1) or (2) a group of semisynthetic cellulose derivative polymers (Table 2). The interactions noted in Tables 1 and 2 fall into four categories: whether a supersaturated state was stabilized or not, if an increase in aqueous solubility was reported, if hydrogen bonding was detected, and if modification of the crystal habit of the precipitate was observed. In all instances of these observed interactions, as noted by Usui et al. (1997), the polymers were not incorporated into the crystal structure of the precipitated drug. A number of different classes of polymers have been screened for their ability to produce a metastable supersaturated solution, the focus being predominately on PVP, HPMC, and other associated cellulose derivatives. Specific observations involving the most common polymers classes are summarized below.

Polyvinylpyrrolidone

PVP has been reported to stabilize the supersaturated state of the following drugs *in vitro*: bicalutamide (Lindfors et al., 2008), compounds 4 and 5 (Curatolo et al., 2009), danazol (Erlich et al., 1999), EMD 57033 (Vogt et al., 2008a), itraconazole (Miller et al., 2008), nifedipine (Suzuki and Sunada, 1998a; Tanno et al., 2004), salicylic acid and its derivatives (Plaizier-Vercammen, 1983), and tacrolimus (Yamashita et al., 2003).

The inhibition of precipitation by PVP appears to be drug-dependent, with no supersaturation observed for albendazole, danazol, felodipine (Vogt et al., 2008b), and fenofibrate (Vogt et al., 2008a). In most studies where an effect has been observed, it appears to reflect a reduction in the growth kinetics. A reported exception is the precipitation of paracetamol, where PVP introduced a lag time to nucleation (Garekani et al., 2000).

Lindfors et al. (2008) examined the homogeneous nucleation process of bicalutamide in the presence of PVP and concluded that PVP changed the crystal growth rate, but not the nucleation rate. This conclusion was reached based on the finding that in the absence of polymer, above a bicalutamide concentration of 300 μM the solution concentration dropped rapidly to the equilibrium solubility of 14.5 μM, which was the same final concentration reached both in the presence and absence of the polymer. In the presence of PVP, above 300 μM crystals were still observed; however, the aqueous concentration at various times was significantly higher. This suggested that the system had yet to reach equilibrium and that the polymer had influenced the precipitation kinetics. Modeling of the kinetics determined that the rate constant of the surface integration step of drug molecules with growing crystals was decreased by the presence of PVP. Lindfors et al. (2008) also determined that PVP interacted strongly with bicalutamide, as evidenced by the adsorption of 3.3 mg/m^2 of PVP onto preformed bicalutamide crystals and a decrease in the self-diffusion coefficient of bicalutamide in the presence of PVP.

In some cases, the effects of PVP have been shown to be dependent on polymer MW. For example, higher MW polymers were shown to be more efficient in complexing salicylic acid and its derivatives (Plaizier-Vercammen, 1983) and improving the kinetic stability of supersaturated solutions of itraconazole (Miller et al., 2008).

Cellulose derivatives

A diverse range of cellulose derivatives are available for use in solid dosage forms, sustained release dosage

Table 1. Interactions between miscellaneous polymers and small molecules, including drugs.

Polymer name (trade/ abbreviation/alternative)	Interaction				No interaction
	Stabilized supersaturation	Increased aqueous solubility	Hydrogen bonding	Modified crystal habit	Supersaturation not Stabilized
Poly (acrylic acid) (PAA)	Caffeine (Gift et al., 2008) CR Calcium sulfate (Lioliou et al., 2006) AP Calcium sulfate dihydrate (Smith and Alexander, 1970) AP			Calcium carbonate (Donnet et al., 2010) Calcium oxalate (Doherty et al., 2004) Calcium sulfate (Lioliou et al., 2006) Potassium sulfate (Oaki and Imai, 2005)	Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP
Polyether polyol				Potassium dihydrogen phosphate (Machefer et al., 2008)	
Polyethylene imine (PEI)	Compound 9 (Curatolo et al., 2009) # SP				Danazol (this study) SP
Polyethylene oxide (PEO), polyethylene glycol (PEG)		Griseofulvin (Chiou, 1977)	Acetaminophen (Wen et al., 2005) AP Felodipine (Teberekidis and Sigalas, 2007) SD	Mebendazole (Kumar et al., 2008b) Paracetamol (Kachrimanis and Malamataris, 1999)	Compound 9 (Curatolo et al., 2009) # SP Estradiol (Megrab et al., 1995) SP
Poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) (PEO-PPO-PEO, Pluronic, poloxamer)	Celecoxib (Guzmán et al., 2007) SD	Diazepam (Lin and Yang, 1987) Nifedipine (Chutimaworapan et al., 2000)	Nifedipine (Chutimaworapan et al., 2000) SD	Molybdenum oxide (Munoz-Espi et al., 2008)	Acetaminophen (Ziller and Rupprecht, 1988) TC Celecoxib (Guzmán et al., 2007) SD Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP Tacrolimus (Overhoff et al., 2008) SD
Polyvinyl alcohol (PVA)	Caffeine (Gift et al., 2008) CR Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP Hydrocortisone acetate (Raghavan et al., 2001a) SP Estradiol (Megrab et al., 1995) SP Tacrolimus (Overhoff et al., 2008) SD		Acetaminophen (Wen et al., 2005) AP	Ammonium perchlorate (Vargeese et al., 2008) Calcium carbonate (Kim et al., 2005).	Nifedipine (Suzuki and Sunada, 1998a, b) SD
Polymethylacrylate (Eudragit, PMA)	Calcium sulfate dihydrate (Smith and Alexander, 1970) AP Danazol (this study) SP Itraconazole (Overhoff et al., 2007; Miller et al., 2008) SD Nifedipine (Kondo and Sugimoto, 1987; Tanno et al., 2004) SD			Calcium sulfate dihydrate (Oner et al., 1998) Ibuprofen (Kachrimanis et al., 1998; Kachrimanis et al., 2000) Nimesulide (Mallick et al., 2004) Mebendazole (Kumar et al., 2008b)	Nifedipine (Kondo and Sugimoto, 1987; Tanno et al., 2004) SD
Polystyrensulfonic acid (PSSA)	Sodium bicarbonate (Martinez-Cruz et al., 2004) TC			Calcium carbonate (Kawaguchi et al., 1992) Sodium bicarbonate (Martinez-Cruz et al., 2004)	

Table 1. continued on next page

Table 1. Continued.

Polymer name (trade/ abbreviation/alternative)	Interaction				No interaction
	Stabilized supersaturation	Increased aqueous solubility	Hydrogen bonding	Modified crystal habit	Supersaturation not Stabilized
Polyvinyl acetate phthalate (PVAP)	Compound 2 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP Itraconazole (DiNunzio et al., 2008) SD		Itraconazole (DiNunzio et al., 2008) SD		
Polyvinylpyrrolidone (PVP, Kollidon, Polyplasdone)	Acetaminophen (Ziller and Rupprecht, 1988) AP Bicalutamide (Lindfors et al., 2008) SP Carbamazepine (Gift et al., 2008) CR Compound 4 (Curatolo et al., 2009) # SD Compound 5 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP Danazol (Erlich et al., 1999) LF Danazol (this study) SP EMD 57033 (Vogt et al., 2008a, Vogt et al., 2008b) SD Felodipine (Konno et al., 2008; Alonzo et al., 2010) SD AM Hydrocortisone acetate (Raghavan et al., 2001a, Raghavan et al., 2001b) SP Indomethacin (Alonzo et al., 2010) AM Nifedipine (Suzuki and Sunada, 1998a, b; Tanno et al., 2004) SD Estradiol (Megrab et al., 1995) SP Paracetamol (Garekani et al., 2000) SP RS-8359 (Usui et al., 1997) SP Sulfamerazine (Sekikawa et al., 1978b) SP Sulfamethizole (Sekikawa et al., 1978b) SP Sulfisoxazole (Sekikawa et al., 1978a, Sekikawa et al., 1978b) AP Tacrolimus (Yamashita et al., 2003; Overhoff et al., 2008) SP SD 10 Unidentified (Vandecruys et al., 2007) SP	Acetazolamide (Loftsson et al., 1996) Chlorothiazide (O'driscoll and Corrigan, 1982) Felodipine (Karavas et al., 2006) Hydrocortisone (Loftsson et al., 1996) Hydrocortisone acetate (Raghavan et al., 2001a) Indomethacin (Hilton and Summers, 1986) Parazepam (Loftsson et al., 1996) RS-8359 (Usui et al., 1997) Sulfamethoxazole (Loftsson et al., 1996) Sulfathiazole (Simonelli et al., 1976) Valdecoxib (Bansal et al., 2007)	Felodipine (Karavas et al., 2007; Teberekidis and Sigalas, 2007) SD Hydrocortisone acetate (Raghavan et al., 2001a) SD Indomethacin (Taylor and Zografi, 1997) SD SB-210661 (Perng et al., 1998) SD	Bicalutamide (Lindfors et al., 2008) Mebendazole (Kumar et al., 2008b; Kumar et al., 2008a) Paracetamol (Kachrimanis and Malamataris, 1999; Garekani et al., 2000) Zinc oxide (Liu et al., 2006)	Albendazole (Vogt et al., 2008a, Vogt et al., 2008b) SD Danazol (Vogt et al., 2008a, Vogt et al., 2008b) SD Felodipine (Vogt et al., 2008a, Vogt et al., 2008b) SD Fenofibrate (Vogt et al., 2008a) SD
Polyvinylpyrrolidone-*co*-polyvinyl acetate (PVPVA)	Itraconazole (Janssens et al., 2008) SD 14 Unidentified (Vandecruys et al., 2007) SP				

SD, solid dispersion; LF, lipid formulation; AM, amorphous; CR, crystalline; SP, solvent phase; TC, temperature change; AP, aqueous phase; all denote the state of supersaturation generated by the system, or the phase interaction detected within.

Table 2. Interactions between cellulose-derived polymers and small molecules, including drugs.

	Interaction				No interaction
Polymer name (trade/ abbreviation/alternative)	Stabilized supersaturation	Increased aqueous solubility	Hydrogen bonding	Modified crystal habit	Supersaturation not stabilized
Cellulose acetate phthalate (CAP)	Compound 4 (Curatolo et al., 2009) # SD Compound 5 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP Itraconazole (DiNunzio et al., 2008) SD				
Carboxymethyl cellulose (CMC)					Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP
Methyl cellulose (MC, Methocel, Benecel, Metolose)	Danazol (this study) SP Hydrocortisone acetate (Raghavan et al., 2000, 2001a, b) SP Itraconazole (Miller et al., 2008) SD				
Hydroxyethyl cellulose (HEC)	Danazol (this study) SP		Acetaminophen (Wen et al., 2005) AP		
Hydroxyproply cellulose (HPC, Klucel)	Carbamazepine (Gift et al., 2008) CR Celecoxib (Guzmán et al., 2007) SD Compound 2 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP Estradiol (Megrab et al., 1995) SP RS-8359 (Usui et al., 1997) SP 8 Unidentified (Vandecruys et al., 2007) SP	Celecoxib (Guzmán et al., 2007) SD RS-8359 (Usui et al., 1997)	Acetaminophen (Wen et al., 2005) AP	Erythromycin A dehydrate (Mirza et al., 2009) Mebendazole (Kumar et al., 2008a, Kumar et al., 2008b)	
Hydroxypropylmethyl cellulose (HPMC, hypromellose, Methocel, Benecel, Pharmacoat)	Albendazole (Kohri et al., 1999) SD AMG 517 (Gao et al., 2009) LP Carbamazepine (Gift et al., 2008) CR Cefditoren pivoxil (Yokoi et al., 2005) SD Celecoxib (Guzmán et al., 2007) SD Compound 4 (Curatolo et al., 2009) # SD Compound 5 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP Drug X (Gao and Morozowich, 2006) LP EMD 57033 (Vogt et al., 2008a, Vogt et al., 2008b) SD ER-34122 (Kushida et al., 2002) SD Felodipine (Konno et al., 2008; Alonzo et al., 2010) SD AM Hydrocortisone acetate (Raghavan et al., 2000, 2001a, b) SP Ibuprofen (Iervolino et al., 2001) SP Indomethacin (Alonzo et al., 2010) AM Itraconazole (Matteucci et al., 2007; Brewster et al., 2008; Miller et al., 2008; Van Speybroeck et al., 2010) SD	Acetazolamide (Loftsson et al., 1996) Hydrocortisone (Loftsson et al., 1996) Parazepam (Loftsson et al., 1996) RS-8359 (Usui et al., 1997) Sulfamethoxazole (Loftsson et al., 1996)	Acetaminophen (Wen et al., 2005) AP ER-34122 (Kushida et al., 2002) SD Felodipine (Konno and Taylor, 2006) SD Ibuprofen (Iervolino et al., 2001) SD Piroxicam (Pellett et al., 1997a, b) AP	AMG 517 (Gao et al., 2009) Calcium carbonate (Kulak et al., 2007) Carbamazepine (Katzhendler et al., 1998; Tian et al., 2009) Hydrocortisone acetate (Raghavan et al., 2001b) Mebendazole (Kumar et al., 2008a, Kumar et al., 2008b) Nitrofurantoin (Tian et al., 2009) Triclosan (Raghavan et al., 2003)	

Table 2. continued on next page

Table 2. Continued.

Polymer name (trade/ abbreviation/alternative)	Interaction				No interaction
	Stabilized supersaturation	Increased aqueous solubility	Hydrogen bonding	Modified crystal habit	Supersaturation not stabilized
	Nifedipine (Suzuki and Sunada, 1998a; Tanno et al., 2004) SD Nitrendipine (Suzuki and Sunada, 1998b) SD Estradiol (Megrab et al., 1995) SP Paclitaxel (Gao et al., 2003) LP PNU-91325 (Gao et al., 2004) LP RS-8359 (Usui et al., 1997) SP Tacrolimus (Yamashita et al., 2003; Overhoff et al., 2008) SD 10 Unidentified (Vandecruys et al., 2007) SP				
Hydroxypropylmethyl cellulose phthalate (HPMCP, hypromellose phthalate)	Albendazole (Kohri et al., 1999) SD Compound 5 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP Danazol (this study) SP Itraconazole (Overhoff et al., 2007; Miller et al., 2008) SD Nifedipine (Kondo and Sugimoto, 1987; Tanno et al., 2004) SD				
Hydroxypropylmethyl cellulose acetate succinate (HPMCAS, hypromellose acetate succinate, AQOAT)	Compound 1 (Curatolo et al., 2009) # SD Compound 2 (Curatolo et al., 2009) # SD Compound 3 (Curatolo et al., 2009) # SD Compound 4 (Curatolo et al., 2009) # SD Compound 5 (Curatolo et al., 2009) # SD Compound 9 (Curatolo et al., 2009) # SP SD Danazol (this study) SP Felodipine (Konno et al., 2008; Alonzo et al., 2010) SD AM Griseofulvin (Curatolo et al., 2009) SD Itraconazole (Van Speybroeck et al., 2010) Nifedipine (Tanno et al., 2004; Curatolo et al., 2009) SD Phenytoin (Curatolo et al., 2009) SD Sildenafil citrate (Appel et al., 2006) SD Torceptrapib (Friesen et al., 2008) SD Ziprasidone (Appel et al., 2006) SD		Felodipine (Konno and Taylor, 2006) SD		

SD, solid dispersion; LF, lipid formulation; AM, amorphous; CR, crystalline; SP, solvent phase; TC, temperature change, AP, aqueous phase; all denote the state of supersaturation generated by the system, or the phase interaction detected within.

Compound:

1 = 3,6-Dimethyl-4-(3-pentoxy)-2-(2,4,5-trimethylphenoxy)pyridine.

2 = [*R*-(*R**,*S**)]-5-chloro-*N*-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl]-1*H*-indole-2-carboxamide.

3 = 5-Chloro-1*H*-indole-2-carboxylic acid [(1*S*)]-benzyl-(2*R*)-hydroxy-3-((3*R*,4*S*)-dihydroxy-pyrroloidin-1-yl-)-3-oxypropyl]amide.

4 = 5-Chloro-1*H*-indole-2-carboxylic acid [(1)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxy-ethyl]-amide.

5 = 2-Phenanthrenecarboxaimde,4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-,(4b*S*,7*S*,8a*R*)-.

9 = 2-(4-Ethoxybenzyl)-1,2-dihydroimidazo[1,5-*a*] quinoxalin-3(5*H*)-one

forms, and applications of film coating. In recent years, these polymers have also been studied as inhibitors of crystallization.

Hydroxypropylmethyl cellulose

HPMC has been the most extensively studied PPI and is perhaps the most encouraging candidate PPI to this point. HPMC has been found to perform well across a wide range of drugs, including albendazole (Kohri et al., 1999), AMG 517 (Gao et al., 2009), cefditoren pivoxil (Yokoi et al., 2005), celecoxib (Guzmán et al., 2007), compounds 4, 5, and 9 (Curatolo et al., 2009), Drug X (Gao and Morozowich, 2006), EMD 57033 (Vogt et al., 2008a, b), ER-34122 (Kushida et al., 2002), hydrocortisone acetate (Raghavan et al., 2001a), ibuprofen (Iervolino et al., 2001), itraconazole (Matteucci et al., 2007; Brewster et al., 2008; Miller et al., 2008), nifedipine (Suzuki and Sunada, 1998a; Tanno et al., 2004), nitrendipine (Suzuki and Sunada, 1998b), estradiol (Megrab et al., 1995), paclitaxel (Gao et al., 2003), PNU-91325 (Gao et al., 2004), and tacrolimus (Yamashita et al., 2003).

HPMC is a broad-spectrum PPI with a remarkable lack of drug specificity. *In vitro* and *in vivo* precipitation inhibition by HPMC has been demonstrated for itraconazole (Miller et al., 2008), paclitaxel (Gao et al., 2003), tacrolimus (Yamashita et al., 2003; Overhoff et al., 2008), and an unidentified compound (Vandecruys et al., 2007).

HPMC acetate succinate

In more recent studies (Appel et al., 2006; Friesen et al., 2008; Curatolo et al., 2009), focus has shifted from HPMC to HPMC acetate succinate (HPMCAS), which has been identified as a superior PPI for many drugs with a wide variety of structures and physical properties. HPMCAS has been reported to stabilize the supersaturated state of compounds 1–5 and 9 (Curatolo et al., 2009), griseofulvin (Curatolo et al., 2009), nifedipine (Tanno et al., 2004; Curatolo et al., 2009), phenytoin (Curatolo et al., 2009), sildenafil citrate (Appel et al., 2006), torceptrapib (Friesen et al., 2008), and ziprasidone (Appel et al., 2006). Both Curatolo et al. (2009) and Friesen et al. (2008) concluded that the superior inhibition was due to two properties of HPMCAS: first above pH 5 it is partially ionized, supporting stabilized nanosized amorphous drug–polymer aggregates; and second it contains hydrophobic regions, providing sites for drug molecule association. The generation and maintenance of nanosized drug–polymer aggregates has been identified as a key factor, providing a reservoir from which the drug can dissolve and maintain the supersaturated free-drug concentration.

Poloxamers

The poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) (poloxamer, P-EPE) polymers have typically been found to be very poor PPIs, although a limited selection of P-EPE have been suggested to inhibit the precipitation of celecoxib (Guzmán et al., 2007). In all other cases, acetaminophen (Ziller and Rupprecht, 1988), celecoxib (Guzmán et al., 2007), compound 9 (Curatolo et al., 2009), danazol (this study), and tacrolimus (Overhoff et al., 2008), precipitation inhibition by P-EPE has not been observed. The lack of precipitation inhibition may be attributed to the inability of P-EPE to act as a hydrogen bond donor. However, there are some exceptions to this and it appears to be highly drug-specific. For example, no hydrogen bonding was observed between Pluronic P188 and ibuprofen in a solid dispersion under conditions above the drug pK_a, where predominately hydrogen bond acceptors were present on the drug molecule (Newa et al., 2007). Conversely, hydrogen bonding was detected in a solid dispersion between a poloxamer and nifedipine, a drug that only contains hydrogen bond acceptors (Chutimaworapan et al., 2000).

Change of crystal habit

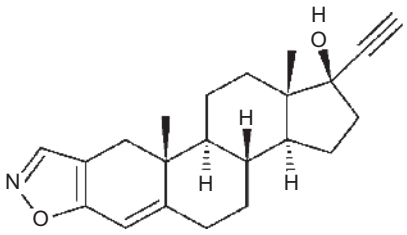
As shown in Tables 1 and 2, modification of crystal habit in the presence of PPIs is a common occurrence. The change in crystal habit, as indicated in the section titled "Precipitation/crystallization" and "Crystal habit and impurities," has been shown by Guo et al. (2002) to be due to the selective adsorption of the polymer to different crystal faces. Guo et al. also reported that several polymeric additives were effective inhibitors of both crystal growth and dissolution of calcium oxalate monohydrate. There has been only one reported incidence when the presence of a PPI resulted in the formation of an amorphous drug precipitate. Gao et al. (2009) reported that AMG 517 formed amorphous drug when precipitated in the presence of HPMC, whereas crystalline drug precipitated in the presence of PVP.

Recent data on the interaction between PPIs and danazol

Currently, there is a lack of understanding of the molecular basis for the interactions that occur between PPIs and drug molecules, and of the mechanisms of precipitation inhibition for many of these polymers. A better understanding of these processes, however, is expected to facilitate more intelligent selection of the appropriate PPI for a specific drug molecule. Previous studies have provided a good starting point to the generation of this critical dataset; however, the available database remains small. In order to obtain the fundamental information required to address this problem, we therefore recently initiated a study of PPI using a wide variety of polymer classes and a selection of model drugs. To expand the dataset available for review in the current article, we present here the preliminary results of this study and the methods employed to generate the data. Danazol was selected as a model drug (properties shown in Table 3) for these studies since it is well-characterized, poorly water-soluble, nonionized, and has low solubility limited oral bioavailability.

In these studies, the co-solvent quench method was used to generate a supersaturated state of danazol in

Table 3. Structure and physical properties of danazol.

Molecular structure	
Molecular weight	337.5 g/mol
Solubility (25°C)	
Water	0.58 μg/mL (Erlich et al., 1999)
	1 μg/mL (Alsenz et al., 2007)
Propylene glycol	9.05 mg/mL (Alsenz et al., 2007)
	10.8 mg/mL (Erlich et al., 1999)
Log*P*	3.927 (Alsenz et al., 2007)
	4.2 (Clarysse et al., 2009)
	4.53 (Bakatselou et al., 1991)

an aqueous phase containing polymer, and the effects of polymers on danazol precipitation over a range of concentration (0.001% and 0.1% w/v) explored. This concentration range represents the likely minimum and maximum concentration that would be expected to be present in the lumen of the GI tract after dispersion of an oral dosage form. This simplified approach was selected to remove other phenomena, such as the dispersion and dissolution required from a solid or lipid phase following its addition to the aqueous phase. This method does not model all of the processes that may occur in a physiological system; however, it allows isolation of the effect of the polymer on inhibition of drug precipitation. The data was obtained by monitoring the turbidity of the supersaturated system, allowing collection of detailed data on the kinetics of precipitation *in situ*.

Materials and methods

Materials

The following polymers were obtained from Sigma-Aldrich Pty Ltd., Australia: CAP, alginic acid, gum Arabic, locust bean gum, xanthan gum, HPMC, methyl 2-hydroxyethyl cellulose (MHEC), poly(acrylic acid) (PAA) 1.8, 1250, and 3000, polyallylamine hydrogen chloride (PAAH), poly(acrylamide-*co*-acrylic acid) (PAC-AC) 200 and 5000, polydiallyldimethylammonium chloride (PDDA), polyethyleneimine (PEI), poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) (P-EPE) 1100 and 14,600, poly(2-ethyl 2-oxazoline) (PEOX), polyvinyl alcohol (PVA) 50 and 94, PVP 10, 40, 360, and cross-linked PVP. HPMC E4M was supplied by The Dow Chemical Company, c/o Colorcon Asia Pacific Pty Ltd., Australia. Hercules Chemical Company Inc., c/o APS Healthcare, Nuplex Industries Pty Ltd Australia supplied the following polymers: ethyl cellulose N100 (EC), hydroxyethyl cellulose (HEC) 250GF, HPC HXF, HPMC K200M and K4M, methyl cellulose (MC) A4C, and sodium carboxymethyl cellulose (SCMC) 7H, 9M, and 12M. HEC 30000 was supplied by Shandong Head Co. Ltd. and Carbomer 340 and 934 by Suichang Tinci Materials Technology Co. Ltd., all c/o Ceechem Pty Ltd., Australia. Eudragit E100, L100, L100-55, RL100, and S100 were supplied by Evonik Degussa Australia Pty Ltd., and HPMC 606 and 904, HPMCAS Lf, MF, and HF by ShinEtsu Chemical Co. Ltd., c/o ANZChem Pty Ltd., Australia.

Danazol was supplied by Sterling Pharmaceuticals (Sydney, Australia). Analytical grade sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride were used for the aqueous phase buffer. Propylene glycol was obtained from Merck Pty Ltd., Australia.

Turbidity measurement

The aqueous phase was buffered to pH 6.5, using 18 mM NaH_2PO_4 and 12 mM Na_2HPO_4 as the pH buffer, and adjusted to an ionic strength of 0.152 M using 98 mM NaCl. These were same buffer conditions used previously for simulated endogenous intestinal fluid (Kossena et al., 2004). The co-solvent phase was propylene glycol containing 1 mg/cm^3 of danazol. Three hundred microliters of the co-solvent containing drug were thoroughly mixed in 3000 μL of aqueous phase (producing a degree of supersaturation of ~150). Four 300 μL samples of this dispersion were pipetted into individual wells of a 96-well microplate, which was introduced into nephelometer. The delay between mixing of the solution and the first nephelometer measurement was recorded (within the region of 30–60 s). Blanks were also run in parallel, consisting of propylene glycol, without the dissolved danazol, mixed with the aqueous phase. All measurements were performed at 20°C.

The polymer concentrations within the aqueous phase tested were 0.001% and 0.1% w/v. This range was selected based on the approximate physiological concentration of 0.02% w/v obtained when a 1 g tablet/liquid capsule containing 5% w/w polymer is dispersed within 250 mL aqueous phase in the stomach.

The drug precipitation was monitored using a NEPHELOstar Galaxy (BMG Labtechnologies) microplate nephelometer by measuring the turbidity of the solutions, with a $\lambda = 635$ nm laser. The nephelometer program settings used were: gain = 70, cycle time = 30 s, measurement time per well = 0.30 s, positioning delay 0.5 s; orbital shaking was employed with a width of 2 mm for 5 s at the end of each cycle. The 96-microwell plates made from polystyrene with flat-bottomed wells (NUNC) were used.

Classification of precipitation data

The nephelometer produced signal versus time data, with the signal providing a measure of the amount of precipitate present. A classification system was developed to group the signal versus time curves and to simplify the analysis. A total of seven different curves were observed,

which were grouped into three characteristic types: Types A, B, and C, as shown in Figure 7.

Type A

Type A precipitation was characterized by significant inhibition of precipitation for the entire period of the experiments (1.5 h/5400 s), see Figure 7A. Type A was further divided into two subtypes: Type A1, where precipitation was essentially completely inhibited (thus indicating the best-performing polymers) within the detection limits of the technique; and Type A2, where precipitation still occurred at a very slow, but decreasing rate, and failed to reach an asymptotic value. Type A is the preferred behavior of a good PPI.

Type B

Type B was the more complex of the three types, with two or three distinct precipitation regions (see Figure 7B). This group was further divided into three subtypes: Type B1 had a higher initial rate, which then slowed down dramatically, then after a delay, precipitation took off again before reaching an asymptote; Type B2 had an initial lag phase after which precipitation increased and then reached an asymptote; and Type B3 that had a region of initial precipitation, which then accelerated before it also reached an asymptote. If the lag phase is of sufficient length, then a polymer that causes this type of precipitation behavior may be suitable as a PPI.

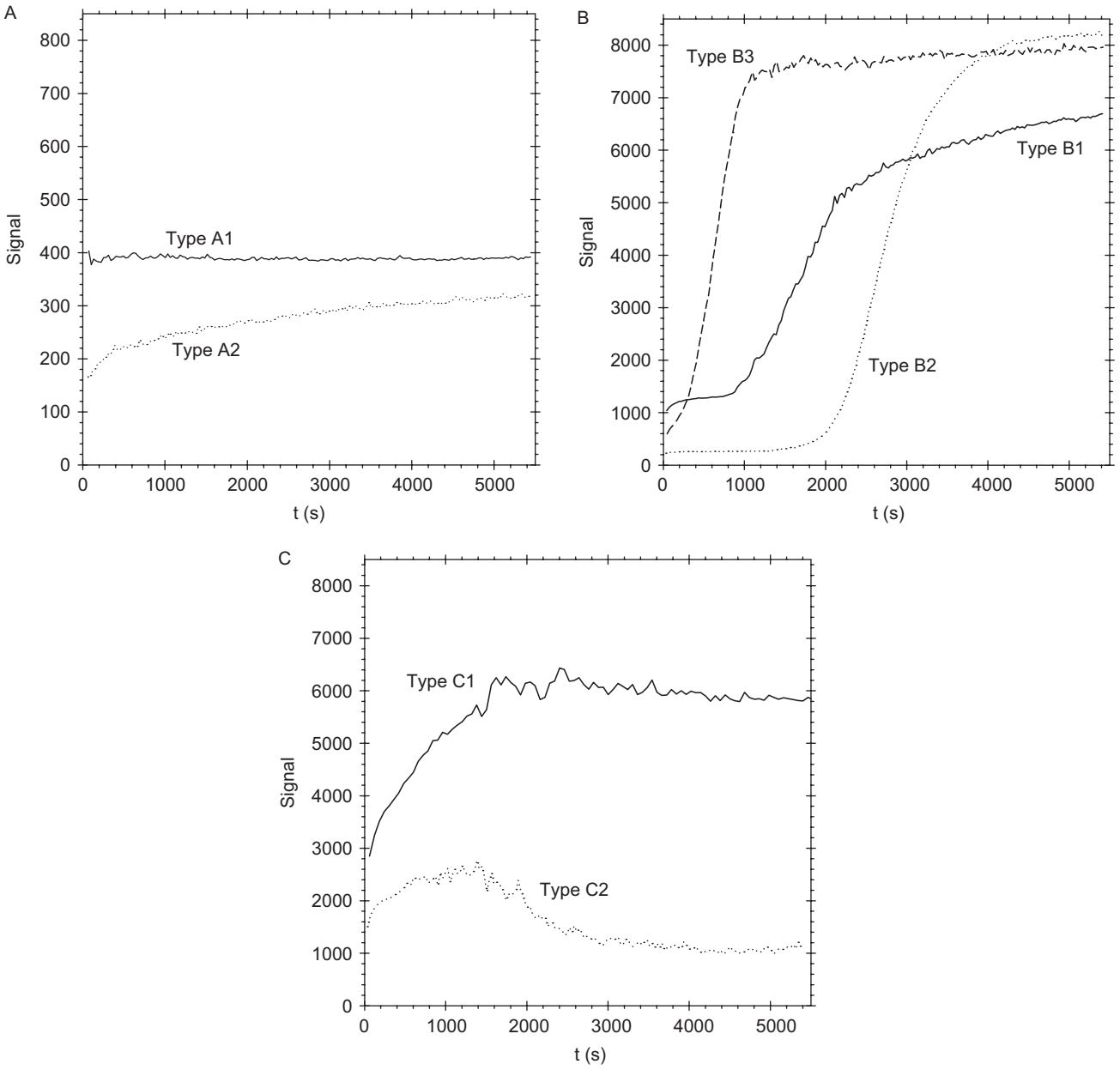


Figure 7. Classification of precipitation types: (A) A1 (—) 0.1% w/v HPMCAS HF and A2 (...) 0.1% w/v HPMC K4M; (B) B1 (—) 0.001% w/v HPMC K4M, B2 (...) 0.001% w/v cellulose acetate phthalate and B3 (---) 0.001% w/v Eudragit L100-55; and (C) C1 (—) no polymer and C2 (...) 0.001% w/v alginic acid. Note that the arbitrary signal values are relative to one another indicating the Type A systems had low turbidity (i.e. there was very limited precipitation) throughout the experiment.

Our current working hypothesis is that Type B1 is the one on which all other types/subtypes are based, that is, all other precipitation profiles represent selected regions of the Type B1 curve with variations in the time scale or rates involved. Further work is underway to link these regions to the physical phenomena involved. The initial interpretation is that the three regions of Type B1 are represented by: nucleation, growth lag, and crystal growth phases.

Type C

Type C precipitation was typified by a high initial rate, which then decreased with time until the signal reached an asymptotic value, at which point precipitation was essentially complete (see Figure 7C). There were two subtypes: Type C1 was typical of precipitation in the absence of any polymer and in the presence of polymers that have no influence on the precipitation process; and Type C2 when flocculation of the precipitate occurred (the signal fluctuated due to formation of large flocs and decreased as flocculation clarified the system). Polymers that promote this characteristic type of precipitation are not suitable as PPIs.

Analysis

The precipitation curve for each system was classified and then the precipitation rate(s) determined by linear regression of parts of the signal versus time curves. An example of a typical Type B1 experiment is shown in Figure 8, indicating how the slopes and time delays were determined.

To enable a quantifiable measure of the performance of the polymers, a relative rate (RR) was calculated using the logarithm (base 10) of the ratio of the precipitation rate (R) to the precipitation rate with no polymer present ($R_{\text{no polymer}}$) (see Equation (1)). The logarithmic scaling was necessary due to the large range of precipitations rates measured from 0.001 to 100 units/s, a spread of five orders of magnitude. Thus, where the rate of precipitation was unchanged in the presence of polymer relative to the rate in the absence of polymer, the RR according to Equation (1) was 0. When the rate is decreased, the RR has a negative value, and a positive value is obtained when the rate is increased. For example, where a RR of –2 is obtained, the precipitation rate has been decreased by a factor of 100.

$$\text{Relative rate} = \log\left(\frac{R}{R_{\text{no polymer}}}\right) \quad (1)$$

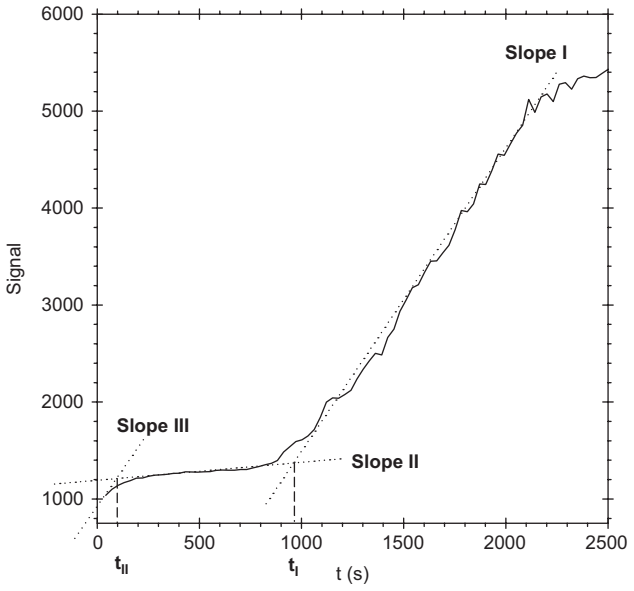


Figure 8. Determination of precipitation rates and delay times from nephelometer experimental data; (—) experimental data, 0.001% w/v HPMC K4M, and (...) fitted curve slopes.

Results

The effects of 53 different polymers from 22 polymer classes on the rates of danazol precipitation from a supersaturated solution were determined and are summarized in Table 4. A representative sample of the raw precipitation data is presented in Figure 9, showing the effect of three polymers: (1) Eudragit L100, (2) gum Arabic, and (3) HPMC E4M at two polymer concentrations (0.001% w/v and 0.1% w/v) on the precipitation process.

The presence of the polymethacrylate (Eudragit L100, Figure 9A) introduced a lag phase to the start of the precipitation process that was concentration-dependent. At 0.001% w/v the lag phase lasted until 420 s, and was pushed out to 3100 s when the concentration was increased to 0.1% w/v. After this lag phase, the precipitation rate, at both concentrations, proceeded at a higher rate than in the absence of the polymer. Eudragit L100 appeared to inhibit the nucleation process, but once that barrier had been overcome the crystal growth phase proceeded as if the polymer was not present. Similar behavior was observed for hydroxypropylmethyl cellulose phthalate (HPMCP)-55S, CAP, PVA 50, PVP, and PEOX, and to a lesser degree Eudragit L100-55, HEC 250GF, and HEC 3000S.

Gum Arabic precipitation profiles (shown in Figure 9B) exhibited no effect on the precipitation process at the low concentration. However, after ~600 s the danazol precipitate and the polymer flocculated, such that the turbidity measurement was no longer valid. This behavior was also observed with other gums, alginic acid, locust bean gum, and xanthan gum. In each case, flocculation made it impossible to monitor any further change in the precipitate concentration. Gum Arabic differed from the other gums in that, at 0.1% w/v, significant precipitation inhibition was observed, decreasing the rate by a factor of 500 (RR = –2.7). Similar precipitation profiles were recorded for the polymers PEI, PAA-AC 200, and PAA-AC 5000.

HPMC E4M, precipitation profiles (shown in Figure 9C), exhibited a lag phase in the precipitation

Table 4. The influence of polymers on the kinetics of danazol precipitation.

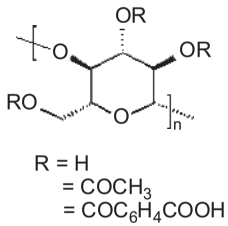
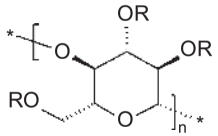
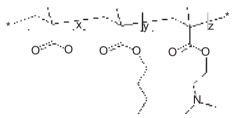
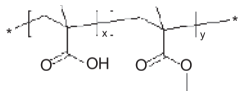
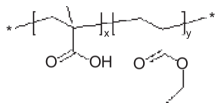
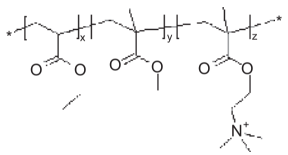
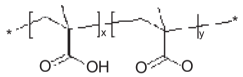
Polymer				Polymer concentration							
				0.001% w/v				0.1% w/v			
				Relative rate and delay time (s)				Relative rate/delay time (s)			
Class	Monomer	Grade	Molecular weight (g/mol)	Slope I (t_I)	Slope II (t_{II})	Slope III	Type	Slope I (t_I)	Slope II (t_{II})	Slope III	Type
None	—	—	—	0.00	—	—	C1	0.00	—	—	C1
Cellulose acetate phthalate	 R = H = $COCH_3$ = COC_6H_4COOH	—	2534	0.04 (2100)	−2.38	—	B2	—	—	−2.29	A1
Carbomer	PAA cross-linked with allyl sucrose or allyl ethers of pentaerythritol	340	Unknown	0.19	—	—	C1	0.50	—	—	C1
		934	Unknown	0.25	—	—	C1	0.10	—	—	C1
Ethyl cellulose	 R = H R = CH_2CH_3	N100	Unknown	0.27	—	—	C1	—	—	—	—
Eudragit		E100	150,000	0.01 (350)	−0.52 (140)	−0.17	B1	—	—	−3.74	A1
		L100	135,000	0.25 (420)	−0.71	—	B3	0.27 (3100)	−2.15 (670)	−1.30	B1
		L100-55	250,000	0.31 (410)	−0.39	—	B3	0.57 (1050)	−0.52	—	B3
		RL100	150,000	0.09	—	—	C1	—	—	—	—
		S100	135,000	0.13	—	—	C1	1.26	—	—	C1

Table 4. continued on next page

Table 4. Continued.

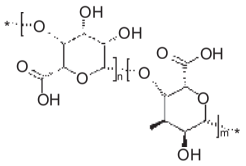
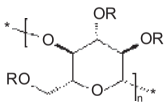
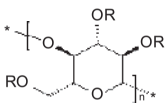
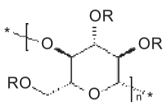
Polymer				Polymer concentration							
				0.001% w/v				0.1% w/v			
				Relative rate/delay time (s)				Relative rate/delay time (s)			
Class	Monomer	Grade	Molecular weight (g/mol)	Slope I (t_I)	Slope II (t_{II})	Slope III	Type	Slope I (t_I)	Slope II (t_{II})	Slope III	Type
Gum		Alginic acid	Unknown	0.89	—	—	C2	−0.78 (3700)	−1.87 (150)	0.46	B1
	Arabinogalactan oligosaccharides, polysaccharides, and glycoproteins	Arabic	250,000	0.88	—	—	C2	—	−2.70 (80)	0.00	A2
	galactomannan	Locust bean	310,000	0.81	—	—	C2	0.54	—	—	C1
	Glucopyranose glucan backbone with mannopyranose, glucuronic acid, and mannopyranose side chains	Xanthan	Unknown	−0.71 (3900)	−0.8862	0.82	B1	−1.13 (4100)	−2.55 (55)	0.41	B1
Hydroxyethyl cellulose	 R = H = $(CH_2)_2OH$	250GF	1,200,000	−0.17 (1300)	−1.35 (220)	−0.34	B1	−0.18 (2400)	−1.77 (460)	−0.93	B1
		30000S	Unknown	0.25 (1100)	−0.94 (290)	−0.57	B1	−0.12 (1100)	−1.20	—	B3
Hydroxypropyl cellulose	 R = H = $(CH_2)_3OH$	HXF	1,150,000	−0.18	—	—	C2	—	—	−2.13	A1
Hydroxypropyl-methyl cellulose	 R = H = CH_3 = $CH_2CH(OH)CH_3$	—	86,000	−0.24 (680)	−0.75 (170)	−0.19	B1	—	−2.27 (840)	−1.73	A2
		606	34,600	0.22 (390)	−0.63	—	B3	—	−2.27 (570)	−1.55	A2
		904	25,200	0.15 (520)	−0.48 (190)	−0.19	B1	—	−2.11 (460)	−1.55	A2
		E4M	86,000	−0.15 (840)	−0.92 (150)	−0.37	B1	—	−2.43 (360)	−1.55	A2
		K200M		0.01 (1100)	−1.56 (190)	−0.72	B1	—	−2.54 (1900)	−1.91	A2
		K4M	340,000	−0.26 (940)	−1.63 (160)	−0.58	B1	—	−2.18 (700)	−0.81	A2

Table 4. continued on next page

Table 4. Continued.

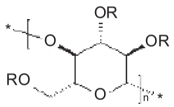
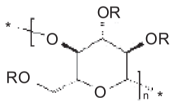
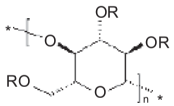
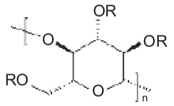
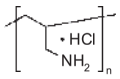
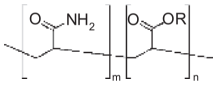
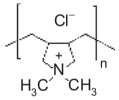
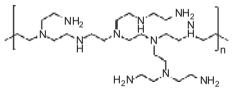
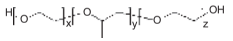
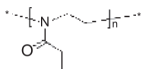
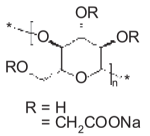
Polymer				Polymer concentration							
				0.001% w/v				0.1% w/v			
				Relative rate/delay time (s)				Relative rate/delay time (s)			
Class	Monomer	Grade	Molecular weight (g/mol)	Slope I (t_I)	Slope II (t_{II})	Slope III	Type	Slope I (t_I)	Slope II (t_{II})	Slope III	Type
Hydroxypropyl-methyl cellulose acetate succinate	 R = H = CH_3 = $CH_2CH(OH)CH_3$ = $COCH_3$ = $CO(CH_2)_2COOH$	LF	18,167	0.04 (1100)	−0.97	—	B2	—	—	−3.75	A1
		MF	17,100	0.31 (420)	−0.90	—	B2	—	−3.20 (510)	−2.03	A2
		HF	17,367	0.04	—	—	C1	—	—	−3.74	A1
Hydroxypropyl-methyl cellulose phthalate	 R = H = CH_3 = $CH_2CH(OH)CH_3$ = COC_6H_4COOH	55S	132,000	0.36 (590)	−1.16	—	B2	−0.36 (830)	−1.52	—	B3
Methyl cellulose	 R = H = CH_3	A4C	86,000	0.24 (550)	−0.50	—	B3	—	−1.90 (350)	−1.37	A2
Methyl 2-hydroxyethyl cellulose	 R = H = CH_3 = $(CH_2CH_2)_xOH$	—	Unknown	—	−3.74 (120)	0.75	A2	—	—	−2.13	A1
Poly(acrylic acid)		1.8	1800	0.24	—	—	C1	0.00	—	—	C1
		1250	1,250,000	0.47	—	—	C1	0.38	—	—	C1
		3000	3,000,000	0.16	—	—	C1	0.18	—	—	C1
Polyallylamine hydrogen chloride		—	15,000	0.78	—	—	C2	—	—	—	—
Poly(acrylamide-*co*-acrylic acid)	 R = H or Na	200	200,000	0.84	—	—	C2	0.64	—	—	C2
		5000	5,000,000	0.93	—	—	C1	0.80	—	—	C1

Table 4. continued on next page

Table 4. Continued.

Polymer				Polymer concentration							
				0.001% w/v				0.1% w/v			
				Relative rate/delay time (s)				Relative rate/delay time (s)			
Class	Monomer	Grade	Molecular weight (g/mol)	Slope I (t_I)	Slope II (t_{II})	Slope III	Type	Slope I (t_I)	Slope II (t_{II})	Slope III	Type
Polydiallyldimethyl-ammonium chloride			150,000	0.77	—	—	C2	0.58	—	—	C2
Polyethylene imine		—	1800	0.85	—	—	C2	0.71	—	—	C2
P-EPE		1100	1100	0.69	—	—	C1	0.69	—	—	C2
		14,600	14,600	0.73 (230)	−0.17	—	B3	−0.14	—	—	C1
		F68	8400	0.73 (200)	0.11	—	B3	0.89	—	—	C1
		L62	2500	0.40	—	—	C1	0.60	—	—	C1
		L64	2900	0.54	—	—	C1	0.50	—	—	C1
		L92	3650	0.46	—	—	C1	0.61	—	—	C1
		P103	4950	0.40	—	—	C1	0.46	—	—	C1
		P105	6500	0.57 (300)	−0.25	—	B3	0.99	—	—	C1
Poly(2-ethyl 2-oxazoline)		50	50,000	0.93	—	—	C1	−0.81 (3300)	−2.62 (210)	0.12	B1
Polyvinyl alcohol		50	50,000	0.09 (550)	−0.37 (160)	0.14	B1	0.87 (440)	−1.44	—	B2
		94	94,000	0.12 (640)	−0.45 (130)	0.20	B1	−0.04 (1000)	−0.93 (220)	0.10	B1
Polyvinylpyrrolidone		10	10,000	−0.56	—	—	C1	−0.55 (3600)	−1.49	—	B3
		40	40,000	−0.46 (1500)	−1.40 (160)	−0.50	B1	−0.17 (3200)	−1.15 (1200)	−0.92	B1
		360	360,000	0.01 (1700)	−0.55	—	B3	−0.66 (4100)	−1.49	—	B3
		Cross-linked	1,000,000	0.16	—	—	C1	−0.05 (860)	−0.91 (230)	−0.29	B1
Sodium carboxyl-methyl cellulose	 R = H = CH_2COONa	7H	1,500,000	0.27	—	—	C1	0.07 (430)	−0.65 (190)	−0.25	B1
		9M	405,000	0.35	—	—	C1	0.11	—	—	C1
		12M	369,000	0.24	—	—	C1	0.11	—	—	C1

Highlighted in blue and green, respectively, are the polymers that are good (−2 < relative rate < −1) and the superior (relative rate< −2) polymeric precipitation inhibitors.

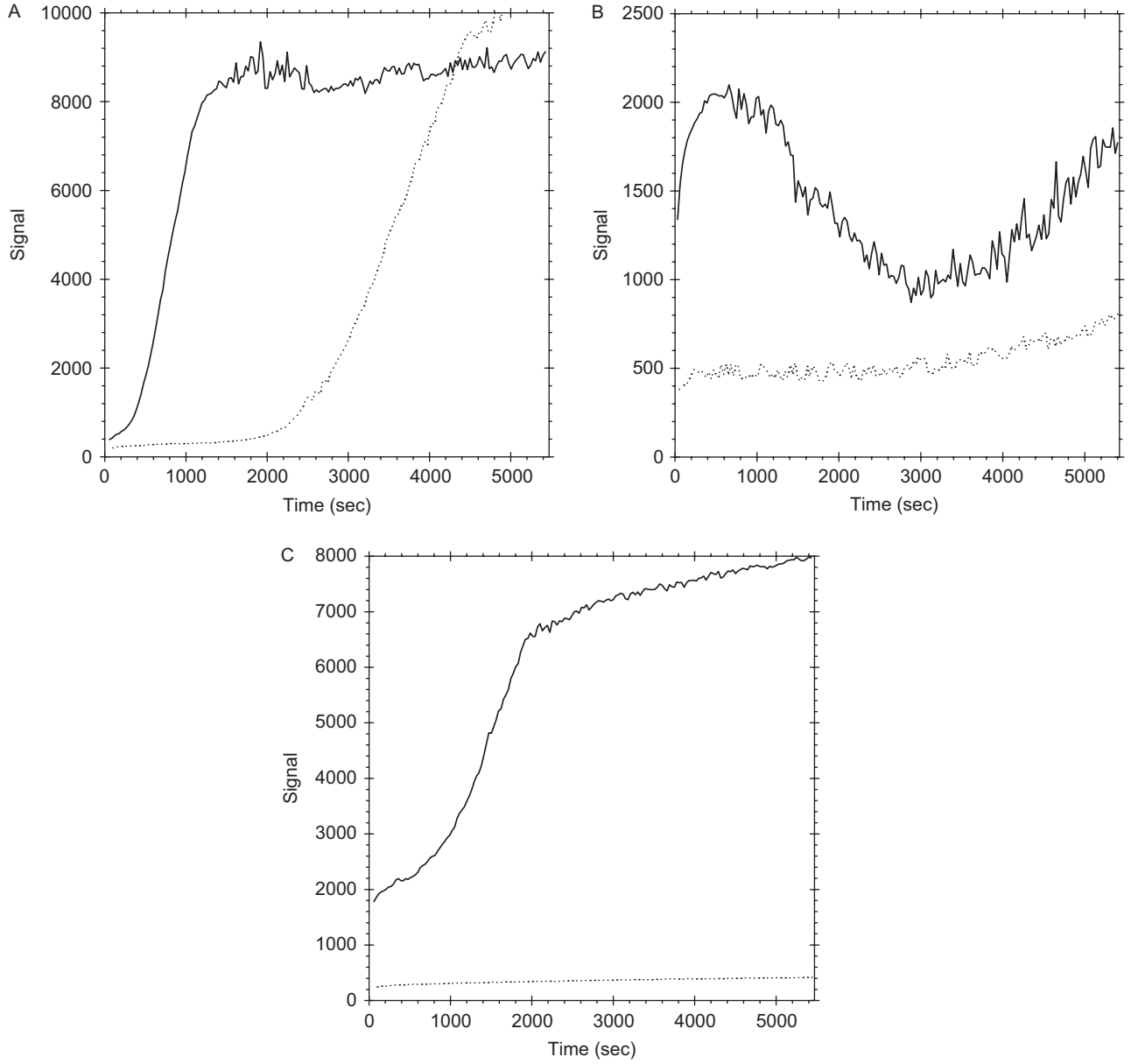


Figure 9. Effect of polymer concentration (—) 0.001% w/v and (...) 0.1% w/v on the precipitation process: (A) Eudragit L100, (B) gum Arabic, and (C) HPMC E4M.

process at 0.001% w/v and a significant decrease of the precipitation rate at all stages (RR = –0.92 to –0.15). When the concentration of polymer was increased to 0.1% w/v, the precipitation was slowed down significantly to RR = –1.55. Similar behavior was observed for all of the HPMC, HPMCAS, and MC grades tested.

Discussion

Due to the complex nature of some of the precipitation profiles obtained, with several rates observed during the duration of the experiments, it is difficult to assign an absolute rank order for polymeric precipitation inhibition at 0.1% w/v. However, the grouping of polymers shown below was assembled based on the relative precipitation rates with the good and superior PPIs for danazol highlighted as blue and green in Table 4, respectively. What is clear from these results is that the superior polymers are cellulose-based, with the exception of Eudragit E100, which is a polymethacrylate.

Enhanced precipitation (RR > 0): carbomer 340, Eudragit S100, locust bean gum, xanthan gum, PAA 1250, PAA 3000, PAAH, PAC-AA 200, PAC-AA 5000, PDDA, PEI, P-EPE 1100, P-EPE F68, P-EPE L62, P-EPE L64, P-EPE L92, P-EPE P103, and P-EPE P105.

No effect (RR = 0): carbomer 934, Eudragit RL100, PAA 1.8, SCMC 9M, and SCMC 12M.

Minor inhibition (0 > RR > –1): Eudragit L100, Eudragit L100-55, alginic acid, P-EPE 14,600, PVA 50, PVA 94, PVP cross-linked, and SCMC 7H.

Good inhibition (–1 > RR > –2): HEC 250GF, HEC 30000S, HPMC, HPMC 606, HPMC 904, HPMC E4M, HPMC K200M, HPMC K4M, HPMCP, MC, PEOX, PVP 10, PVP 40, and PVP 360.

Superior inhibition (–2 > RR): CAP, Eudragit E100, gum Arabic, HPC HXF, HPMCAS LF, HPMCAS MF, HPMCAS HF, and MHEC.

The general rank order of the polymer classes is consistent with previous published data (as shown in Tables 1 and 2), in particular, the data are consistent with the more thorough studies by Vandecruys et al. (2007), Curatolo et al. (2009), and Megrab et al. (1995). Care must be taken with direct comparisons, since the previous studies have all been performed at significantly higher polymer concentrations—a factor of at least 20 to 25 times higher (2% to 2.5% w/v polymer), and the results presented in Table 4 show that a change in polymer concentration can have a dramatic influence on the degree of precipitation inhibition. To generate 2% w/v of polymer within the human stomach would require approximately 0.5–1 g of polymer within the dosage form, which is an upper limit of what is easily accessible. Interestingly, in the current studies, the "superior" PPIs that were identified were not HPMC, which has been the focus of many previous studies rather than other cellulose derivatives.

Direct comparison with Vandecruys et al. (2007) is made difficult since that study examined 25 unidentified drug molecules and five different polymers (HPC, HPMC E5, PVP K30, PVP-*co*-VA, and PEG) at a concentration of 2.5% w/v. Of the five polymers tested, all were found to stabilize at least some of the drugs in the supersaturated state over the test period of 2 h. It is difficult to make more than a qualitative comparison between this study and our data (including the relative efficiency of the polymers) since the identity and properties of the drugs tested are all unknown. Vandecruys et al. (2007) aimed to identify a polymer/excipient that worked with all or most drug molecule conditions rather than to explore the mechanism of action of the PPI. The fact that Vandecruys et al. failed to identify a polymer that worked well with all drug molecules reinforces the view that further work is required to enable a more detailed understanding of the relationship between the polymer, drug, and precipitation inhibition.

Curatolo et al. (2009) preformed a systematic screening of a single drug (2-(4-ethoxybenzyl)-1,2-dihydroimidazo[1,5-*a*]quinoxalin-3(5*H*)-one) against 34 polymers at a concentration of 2% w/v, which generated results that are consistent with the current study. They found that of all the polymers tested, HPMCAS MF was the most effective at maintaining drug in a supersaturated state and that the best-performing polymers were HPMCP-50, HPMC K100, PVP, and PVA, followed by the poorly performing HEC, HPC, and PEI. No inhibition of precipitation was observed when using PAA, CMC, Pluronics (P-EPE), or sodium alginate (sodium salt of alginic acid). The only inconsistency of these results with the current study was their finding that sodium alginate/alginic acid had no inhibitor effects on precipitation; in our study, this polymer had a minor influence on precipitation of danazol. Taken together, the current study and that of Curatolo et al. indicate that there are likely to be some key functional attributes of the most effective PPIs, which are yet to be understood at the molecular level.

Megrab et al. (1995) studied the inhibitory effects of eight polymers (HPMC, HPC, PVA, PEG × 2 and PVP × 3) at a concentration of 2% w/v on the precipitation of estradiol. These authors ranked their PPIs in the order PVP > PVA > HPC > HPMC with PEG being recorded as being ineffective at stabilizing the supersaturated state. Megrab et al. found that HPMC produced only a slight retardation of the crystallization of estradiol, the initial concentration falling to 40% after 6 h. HPC performed better, with 60% of the drug maintained in solution after 6 h, PVA produced substantially improved stability with 80% in solution after 6 h, and PVP was the most effective polymer, maintaining 90% of the drug in solution after 6 h. In the current study, the rank order in relation to precipitation of danazol was quite different (HPC > HPMC > PVP > PVA). The cellulose derivatives were clearly superior to the polyvinyl polymers. These studies taken together suggest that there may be drug-specific effects that are yet to be understood. Megrab et al. also observed that the efficiency of PVP as a PPI for estradiol was at a maximum at a MW of 40,000, and then became less efficient at higher MW. This effect was not observed in the current study with danazol. In fact, the efficiency of PVP as a PPI for danazol went through a minimum at a MW of 40,000. These differences further emphasize that more studies are needed to understand and predict which PPIs are best suited to a particular precipitating drug.

In the current study, an effect of MW was apparent in the HPMC series of polymers when they were separated into low, medium, and high MW (25,000–35,000, 86,000, and 340,000, respectively). The MW of HPMC K200M is currently unknown, but the product number designation (200) indicates that it has a higher viscosity than HPMC K4M (MW = 340,000) and therefore that the MW is likely to be higher than this. As the MW of HPMC was increased, a reduction in the precipitation rate of danazol was observed. This effect was only demonstrable at low concentration. At the higher polymer concentration, the lack of a clear influence on the MW of the polymers indicated that the viscosity of the solution was not the major driving force for inhibition of precipitation.

Conclusions

Drug candidates with low aqueous solubility remain a common product of drug discovery programs. As such drug delivery technologies that can be utilized to support the confident development and marketing of poorly water-soluble molecules continue to be actively sought and evaluated. Over the last several years, great strides

have been taken in this endeavor with the increasingly rational development of polymeric SDF and multicomponent lipid-based formulations. In a continuation of these efforts, recent attention has also started to focus on methods by which a transiently supersaturated state can be generated and maintained *in situ* in the GI tract. This latter approach has two potential benefits: first, maximization of thermodynamic activity, and second, prevention of precipitation and the requirement for redissolution of precipitated drug. Supersaturated solutions are commonly formed via the dissolution of high-energy crystal forms, by gastric emptying of acidic solution of weak bases and by dispersion and digestion of liquid or semisolid formulations containing mixtures of lipids, surfactants, or co-solvents. Whilst the mechanisms by which solute molecules precipitate or crystallize from supersaturated solutions are, in theory, well-developed, the complexity of the GI environment make prediction of precipitation behavior after oral administration difficult. Nonetheless, it is becoming increasingly apparent that supersaturation can be maintained for a finite period by the addition of materials such as polymers, or inorganic materials with high surface area, to the formulation. The exact nature of the interactions that underpin the utility of these materials remains uncertain; however, molecular interactions between drug and polymer, or drug adsorption to a high surface area support, appear to be, at least in part, responsible.

In the current review, we have attempted to pull together the known literature describing the interactions of drug molecules with polymers that lead to a stabilization of supersaturation and a reduction in drug precipitation from supersaturated solution. The current working hypothesis that supports the use of PPIs is that drug supersaturation is stabilized by the presence of drug–polymer interactions (via hydrogen bonding, hydrophobic interactions, or ionic interactions), and/or a decrease in the effective drug diffusion coefficient (in turn influencing the rate of crystallization). We have also described the relative capacities of a series of polymeric materials to impede the progress of danazol precipitation from a supersaturated solution. Using this data, we suggest a number of different modes of drug precipitation and the potential impact of PPI, and identify a group of superior PPIs, which are predominately cellulose-based. Interestingly, this group did not include HPMC that has been the focus of many previous studies. The effect of increases in the MW of HPMC and PVP also indicates that viscosity is not the major driving force for precipitation inhibition (at least for danazol in the presence of these polymers). Collectively, these data and the data from the literature suggest that there are likely to be common functional attributes of "good" PPIs; however to this point, the scarcity of data and the complexity of the GI environment have precluded definition of these attributes beyond a limited number of specific examples. More detailed studies are therefore required to elucidate these mechanisms in detail, in an effort to define the relationships between drugs and polymers that control stabilization.

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Declaration of interest

The authors declare no conflict of interest.

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