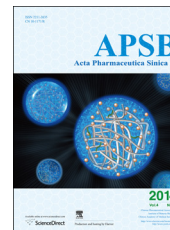




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REVIEW

Crosslinked hydrogels—a promising class of insoluble solid molecular dispersion carriers for enhancing the delivery of poorly soluble drugs

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Abstract Water-insoluble materials containing amorphous solid dispersions (ASD) are an emerging category of drug carriers which can effectively improve dissolution kinetics and kinetic solubility of poorly soluble drugs. ASDs based on water-insoluble crosslinked hydrogels have unique features in contrast to those based on conventional water-soluble and water-insoluble carriers. For example, solid molecular dispersions of poorly soluble drugs in poly(2-hydroxyethyl methacrylate) (PHEMA) can maintain a high level of supersaturation over a prolonged period of time *via* a feedback-controlled diffusion mechanism thus avoiding the initial surge of supersaturation followed by a sharp decline in drug concentration typically encountered with ASDs based on water-soluble polymers. The creation of both immediate- and controlled-release ASD dosage forms is also achievable with the PHEMA based hydrogels. So far, ASD systems based on glassy PHEMA have been shown to be very effective in retarding precipitation of amorphous drugs in the solid state to achieve a robust physical stability. This review summarizes recent research efforts in investigating the potential of developing crosslinked PHEMA hydrogels as a promising alternative to conventional water-soluble ASD carriers, and a related finding that the rate of supersaturation generation does affect the kinetic solubility profiles implications to hydrogel based ASDs.

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1. Introduction

Many new discovery candidates show promising biological activities, but their low oral bioavailability due to poor aqueous solubility has become a major challenge in solid oral dosage form development. There has been significant ongoing research in improving the aqueous solubility of such poorly water-soluble drug candidates, particularly those small molecular weight (MW < 1000 Da) Biopharmaceutics Classification System (BCS) II (high permeability, low solubility) compounds¹. Previous attempts to address this issue employing solubility enhancing approaches through chemical (*e.g.*, pro-drug, salt formation) or physical means (*e.g.*, particle size reduction, complexation/solubilization with cosolvents or surfactants, employing more soluble polymorphs) have not always been successful in accomplishing the desired enhancement in solubility and bioavailability^{2,3}. In contrast, the formation of stabilized amorphous solid dispersions (ASD) in an inert carrier has been shown to be very effective in improving the solubility and bioavailability of poorly water-soluble drugs due to the generation of a transient but highly supersaturated solution concentration (or kinetic solubility) from the ASD, significantly greater than the equilibrium solubility of the crystalline counterpart thus increasing the driving force for its oral absorption. Earlier investigations of incorporating poorly water-soluble drugs in solubilizing agents were mostly on identifying rapidly dissolving small MW carriers (*e.g.*, sulfathiazole-urea⁴) and water-soluble polymer carriers (*e.g.*, sulfathiazole-polyvinylpyrrolidone (PVP)⁵) to improve the drug dissolution rate, the degree of supersaturation, and the oral bioavailability. More recent studies have investigated relevant physicochemical properties of drug-carrier composites that can enhance the stabilization of metastable amorphous drugs in polymeric carriers through their ability to inhibit nucleation and crystal growth in the solid state⁶⁻⁸.

Nevertheless, during dissolution in an aqueous medium, the kinetic solubility profiles of ASDs based on water-soluble polymers generally exhibit an initial surge of drug concentration due to the rapid buildup of supersaturation followed by a sharp decline in drug concentration due to the nucleation and crystallization events triggered by the supersaturation buildup under nonsink dissolution conditions as commonly encountered under finite-volume dissolution conditions in the gastrointestinal (GI) tract. Such a decline in

drug concentration may be retarded to different degrees depending on the ability of the dissolved polymer to inhibit drug precipitation. Moreover, many such rapidly-dissolving hydrophilic polymeric carriers may develop product stability issues due to their hygroscopic nature³. As a result, there has been growing recent interest in exploring the preparation of ASDs in a new category of water-insoluble carriers to enhance stability in the solid state during storage and mitigate the rapid nucleation and crystallization during dissolution thereby producing enhanced kinetic solubility profiles. While previous efforts in applying water-insoluble polymers as drug carriers primarily aimed to achieve controlled release^{9,10}, our group has recently demonstrated the feasibility of employing the biocompatible crosslinked (*i.e.*, water-insoluble) poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogel system as a promising ASD carrier for immediate-release applications^{11,12}. PHEMA has been widely utilized in controlled release drug delivery systems particularly for water-soluble drugs and in biomedical applications such as contact lenses and tissue engineering. Understandably, properties of the polymer matrix play a key role in the dissolution behavior of such drug-carrier composites containing dissolved or dispersed amorphous drugs. The objective of the present review paper is to examine recent research progress in developing crosslinked hydrogels as a new class of effective ASD carriers for poorly water-soluble drugs and to provide an overview of the unique supersaturation kinetics of hydrogel-based ASD systems. To contrast the advantages of using crosslinked hydrogels, a brief survey of known insoluble carriers for amorphous drugs will be first provided.

2. Insoluble carriers for amorphous pharmaceuticals

Physical instability, such as crystallization on ageing, and manufacturing challenges have limited the success in commercial applications of amorphous pharmaceuticals. Since reduced molecular mobility is crucial for the retardation of drug nucleation and crystallization, the selection of suitable carriers is determined by the confinement properties of amorphous drugs. Entrapped drug molecules in polymeric carrier matrices can be classified as crystalline solid dispersion (2-phase system), amorphous solid dispersion (2-phase system) and solid solution (1-phase system) as illustrated in Fig. 1. Compared to the 1-phase solid solution in

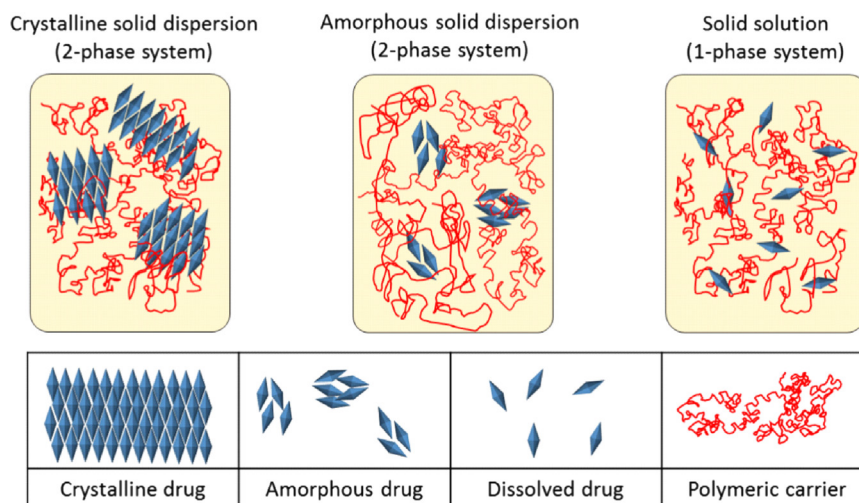


Figure 1 Classification of solid dispersion/solution of drug molecules in polymeric carrier matrix.

which drug molecules are dissolved or molecularly dispersed in the carrier, the 2-phase dispersion systems contain a separated phase of either crystalline (long-range molecular order) or amorphous drugs (short-range molecular order). In reality, formulations based on ASD may also contain a mixture or hybrid of both the 2-phase and 1-phase systems. In the case of nonporous ASD carriers where amorphous drug molecules are completely dissolved (*i.e.*, one-phase solid solution), carriers with extremely low drug diffusivities such as “glassy polymers” (*i.e.*, glass transition temperature, T_g , much higher than the ambient temperature) will exhibit better ASD stability due to hindered drug diffusion and inhibition of drug precipitation in the glassy matrix. The presence of specific drug-carrier intermolecular interactions due to hydrogen bonding, dipole-dipole attraction and van der Waals forces further stabilizes the entrapped amorphous drug preventing it from nucleating and becoming crystalline. On the other hand, in porous carriers where the incorporated bulk amorphous drug is localized in interstitial pore space (*i.e.*, not molecularly dispersed), the nucleation and crystallization of this bulk amorphous drug can give rise to stability issues. However, the drug nucleation and crystallization rates can be reduced if the size of the pore is sufficiently small compared to that of the critical nucleus such that it is energetically unfavorable for nuclei to grow^{13–15}. Table 1 summarizes available water-insoluble carriers utilized to convert poorly water-soluble model drugs into amorphous formulations categorized by their physicochemical characteristics

such as porosity, location of amorphous drug and carrier chemical composition.

For inorganic mesoporous materials such as silica and silicon¹⁶, their large surface area and pore volume can accommodate a larger amount of drug payload. Drug nucleation and crystal growth in the porous channels will be energetically unfavorable if the size of the critical nucleus is larger than that of the pore^{17,18}. In other words, the spatial constraint of a capillary imposed on the amorphous drug below the critical nucleus size provides the stabilizing effect. In addition, a strong interaction with the pore walls (*e.g.*, through hydrogen bonding) further stabilizes the confined drug molecules in an amorphous state and this typically occurs in nano-sized pores with pore diameter smaller than approximately 10 nm¹⁵. The drug loading process in such mesoporous materials commonly involves immersing the carriers in a concentrated drug solution to fill the pores by capillary action followed by the evaporative removal of solvent. One study claims to have successfully accomplished solid dispersion by means of a melt-mixing method, during which a physical mixture of nitrendipine and mesoporous silica particles is heated above the melting point of the drug¹⁸. Nonetheless, in this case the high viscosity of the melted drug can interfere with the capillary action within the pores, potentially causing an incomplete drug loading. Similar constraints also apply to macroporous polymeric carriers such as crosslinked polyvinylpyrrolidone (crospovidone) which exhibits a “popcorn” structure, containing many micron-sized porous cavities, as clearly shown under the SEM^{19–21}.

Table 1 Selected examples of insoluble carriers for amorphous drugs.

Category	Example					
	Carrier ^a	Model Drug	Preparation method ^b	Release mode ^c	Ref.	
I. Non-porous	a. Crosslinked hydrogel	cr-PHEMA hydrogel	Diclofenac sodium, naproxen, piroxicam, indomethacin	S/SE	IR/CR	11,12
		cr-PEO hydrogel	Progesterone	S/SE	CR	25
		Carbopol [®]	Phenacetin	S/SE	CR	26
	b. Water-insoluble polymer	Ethylcellulose	Indomethacin	C/SE	CR	27
		Eudragit [®] RS, RL	Indomethacin, dipyridamole	C/SE	CR	28,29
	c. Lipid	Labrasol and Gelucire 44/14	Piroxicam	HM	IR	30
		Gelucire 44/14 and Gelucire 50/13	Gilbenclamide	C/SE	IR	31
II. Porous	“Popcorn” cr-PVP Silica	Griseofulvin, indomethacin	I/SE, MH	IR	19–21	
		Fenofibrate, carbamazepine, cinnarizine, danazol, ibuprofen diazepam, griseofulvin, indomethacin, ketoconazole, nifedipine, phenylbutazone	I/SE, SD	IR	13,14,32	
		Lovastatin	I/SE	IR	33	
	Starch foam	Lovastatin	I/SE	IR	33	
	Carbon	Celecoxib	I/SE	IR	34	

^aCarrier: cr-PHEMA, poly(2-hydroxyethyl methacrylate) crosslinked with ethylene glycol dimethacrylate; Carbopol[®] (910, 971P, 934P, 974P, 940), polyacrylic acid (lightly crosslinked with allyl sucrose or allyl pentaerythritol); cr-PEO, poly(ethylene oxide) crosslinked with hexamethylene diisocyanate (HMDIC) or tolylene-2,4-diisocyanate (TDIC); cr-PVP, crosslinked polyvinylpyrrolidone; Gelucire 44/14 and 50/13, polyethylene glycol glycerides; Labrasol, caprylocaproyl macrogolglycerides.

^bPreparation method: S/SE, swelling/solvent evaporation; C/SE, cosolvent/solvent evaporation; I/SE, immersion/solvent evaporation; HM, hot melt; MH, mixing and heating ($<T_m$); SD, spray-drying.

^cRelease mode: IR, immediate release; CR, controlled release.

In this case, in addition to the conventional loading method of sorption from a concentrated drug solution, an alternative method of drug loading based on blending or milling of the drug and porous crospovidone particles in the absence of solvent under high mechanical shear for an extended period of time has been proposed^{19,20}. However, the resulting “amorphous” material could be a result of the well-known shear-induced phase transformation at the shear fractured surfaces on drug crystals^{22,23}. As such, the long-term stability of such mechanically generated amorphous systems is questionable because, without any mechanism for crystallization inhibition, this exposed surface amorphous content can easily be converted to the crystalline phase under accelerated temperature and/or humidity conditions.

Alternatively, in nonporous insoluble carrier systems, amorphous drugs can exist as surface adsorbed or molecularly dissolved/dispersed in the matrix depending on the drug loading process. For example, solvent or melt granulation of a poorly soluble drug with a nonporous insoluble carrier typically results in bulk amorphous drug either adsorbed on the carrier surface or unevenly distributed throughout the carrier-drug granule (*i.e.*, a two-phase amorphous solid dispersion). Such surface adsorbed or unevenly distributed bulk amorphous drug lacks the benefit of crystallization inhibition conferred by dissolving or molecularly dispersing the drug in a protective carrier matrix and, therefore, is prone to undesirable nucleation and crystallization events in the solid state. On the other hand, the creation of uniformly dissolved or molecularly dispersed drug in ASD polymeric carriers (*i.e.*, one-phase solid solution) through either drug sorption (*e.g.*, from a good swelling solvent) or coprecipitating from a common organic solvent (*e.g.*, *via* spray drying or freeze drying) is understandably more advantageous than producing dispersed two-phase ASD systems due to its effectiveness in crystallization inhibition and its effect in enhancing the physical stability. For this purpose, applicable nonporous water-insoluble carriers include crosslinked polymers (*e.g.*, PHEMA), cellulose derivatives (*e.g.*, ethylcellulose), and lipids (*e.g.*, PEG-glycerides). The common methods of preparation of ASD based on water-insoluble carriers can be generally classified as supercooling of the melt (*e.g.*, hot-stage melting, hot-melt extrusion), coprecipitating from a common organic solvent (*e.g.*, spray-drying, freeze-drying), and equilibrium sorption (*e.g.*, from a concentrated drug solution prepared in a good swelling solvent) to produce a homogenous binary one-phase system. In this case, the carrier plays an essential role in preserving the entrapped drug molecules in the amorphous state despite the fact that the exact mechanisms of crystallization inhibition in solid molecular dispersions are still not completely understood. Various factors such as molecular mobility, thermodynamic factors, and drug-polymer interactions have been identified as being responsible for inhibiting drug crystallization from the amorphous state^{7,8,24}. Stressed stability conditions involving high relative humidity, high temperature in combination with ageing may accelerate the transformation of metastable amorphous drug in an ASD into more thermodynamically stable crystalline state^{6,24}.

3. Amorphous solid dispersions in crosslinked hydrogels

In selecting an appropriate polymer matrix for an ASD system, the carrier polymer must provide sufficient stabilization effect in the solid state to prevent the entrapped amorphous drug from crystallizing, thereby achieving a reasonable shelf life. From a mechanistic point of view, nucleation and subsequent crystallization of an

amorphous drug in a polymer matrix deplete the local drug concentration around the crystallite and thus triggering drug diffusion from the surrounding amorphous drug region to the crystallite surface to sustain crystal growth. The reduced segmental mobility of polymer chains in glassy PHEMA hydrogels at ambient temperature well below its T_g of 115 °C³⁵ lengthens the polymer molecular relaxation time and retards the diffusional mobility as well as the nucleation and crystallization rates of the entrapped molecularly dispersed drug, thus resulting in enhanced stability of such hydrogel-based solid dispersion systems. An added advantage is that PHEMA hydrogels exist as optically clear glassy solids at ambient temperature, which is suitable for direct microscopic examination for any phase transformation and for the determination of the drug loading threshold in the hydrogel matrix above which amorphous-to-crystalline transition may occur.

In addition to the physical stability of ASDs, the extent of solubility and dissolution enhancement is another key criterion to consider in selecting an appropriate ASD carrier. Typically, kinetic solubility profiles of ASDs based on conventional water-soluble polymers under nonsink dissolution conditions show an instantaneous dissolution causing an initial surge of drug concentration followed by a sharp decline owing to the nucleation and crystallization events triggered by the rapid buildup of drug supersaturation. On the other hand, ASDs based on water-insoluble hydrogels exhibit a unique sustained supersaturation without the initial rapid buildup of supersaturation as will be described in more detail below. For a long while, the kinetics of drug release from crosslinked water-insoluble hydrogels was characterized only in the context of achieving controlled drug release under perfect sink dissolution conditions³⁶, and the application of crosslinked hydrogels as carriers for ASDs was never explored and effect of the hydrogel matrix on the maintenance of supersaturation was virtually unknown. To bridge this gap, our group for the first time employed crosslinked PHEMA hydrogel beads as ASD carriers to enhance the solubility and dissolution rate of poorly soluble drugs suitable for immediate-release oral drug delivery and to investigate the extent of enhancement of kinetic solubility profiles and supersaturation maintenance under nonsink dissolution conditions¹². It was observed that the diffusion-controlled kinetics of drug release from crosslinked PHEMA hydrogels provides a feedback-controlled mechanism to prevent a rapid buildup of supersaturation in the dissolution medium thus avoiding the undesirable nucleation and crystallization events leading to a sharp decrease in drug concentration. This unique diffusion-controlled feedback mechanism regulates the dissolution of entrapped amorphous drugs from the hydrogel matrix to maintain an elevated level of supersaturation for an extended period of time even without the presence of any dissolved polymer or crystallization inhibitor. This aspect and its implications will be discussed in more detail in the following sections.

3.1. Preparation and physicochemical characterization

Based on previously reported protocols³⁷, spherical PHEMA hydrogel beads can be synthesized by a free radical initiated suspension polymerization process. Afterwards, the PHEMA hydrogel beads can be extracted in a Soxhlet with a mixture of water, methanol and ethanol, dried under vacuum before being fractionated and stored in desiccators until use. Although PHEMA is probably the most widely studied gel-forming crosslinked polymer, several other synthetic hydrogels based on nonionic hydrophilic monomers (*e.g.*, hydroxyalkyl

acrylate, *N*-substituted methacrylamides and *N*-vinyl-2-pyrrolidone) are also commonly used in swelling-controlled oral drug delivery³⁸. The drug release kinetics and release rate modulation from such a spherical monolithic diffusion-controlled system have previously been characterized in detail^{39–41}. Chemically, PHEMA has hydrophilic side groups that can promote the sorption of a significantly large amount of polar solvent, thereby providing desired conditions to create solid dispersions with high drug loading. PHEMA can also be easily copolymerized with other hydrophobic monomers, such as methyl methacrylate (MMA) or its homologs, to improve the compatibility of the hydrogel matrix with hydrophobic drugs. Furthermore, the crosslinker chain length and crosslinking density can be adjusted to affect the network mesh size which provides further control of the diffusional drug release⁵⁹. Thus, PHEMA is a good candidate drug carrier because of the ease in regulating drug release by controlling particle size, crosslinking density, chemical composition (*e.g.*, copolymers) and water sorption rate to achieve different drug loading levels and release profiles suitable for oral drug delivery.

ASD in PHEMA hydrogels with various levels of drug loading can be achieved by equilibrating purified PHEMA beads in a concentrated drug solution prepared in a good swelling solvent (*e.g.*, ethanol). Subsequent filtration, rinsing and vacuum drying after the equilibrium sorption process result in glassy hydrogel beads containing uniformly dissolved or dispersed drug. This preparation method involving swelling, drug sorption, followed by solvent evaporation requires the evaporative removal of only a limited amount of solvent imbibed into the hydrogels during the drug loading process, thereby significantly reducing the amount of organic solvent usage comparing to that of the conventional spray drying process for ASDs based on water-soluble polymers where the removal of 90% *w/w* or more organic solvent is typically required. Thus far, ASDs of model poorly water-soluble drugs such as diclofenac sodium, naproxen, piroxicam and indomethacin have been successfully incorporated in PHEMA hydrogels with a maximum drug loading up to approximately 40–50% *w/w*^{11,12}. For example, indomethacin-loaded PHEMA hydrogel beads at various drug loading levels as a function of crosslinking agent concentration and loading solution concentration are shown in Fig. 2, where a transition of physical appearance from being pale yellow and transparent (*i.e.*, containing dissolved drug) to opaque (*i.e.*, containing precipitated drug) when the drug loading exceeds a threshold of approximately 40% *w/w* indomethacin. Representative surface and cross-sectional SEM images of Fig. 3 illustrate that both pure PHEMA and indomethacin-loaded PHEMA hydrogel beads appear to be homogenous and nonporous in morphology in the interior without any significant surface irregularities. The physical state (*e.g.*, amorphous or crystalline polymorph) of the loaded drug can be confirmed by the presence of certain characteristic peaks in the X-ray diffraction (XRD) patterns of the drug-loaded hydrogel beads. A threshold drug loading level of up to 30%–40% *w/w* typically exists in PHEMA hydrogels above which amorphous-to-crystalline transition tends to occur^{11,12}. No drug melting endotherms were detected from the differential scanning calorimetry (DSC) thermograms of drug-PHEMA ASD samples below such threshold drug loading level, reflecting the existence of a completely amorphous phase of dissolved drug in the hydrogel matrix. The thermal analysis by DSC also shows that the T_g of drug-PHEMA ASD decreases as the drug loading increases due to the plasticizing effect of dissolved drug on the polymer network (*i.e.*, PHEMA has a T_g much higher than that of the model drugs). In addition, spectroscopic analysis by fourier transformed infrared (FTIR) was used to confirm the presence of

hydrogen bonding between the drug and the polymer in diclofenac sodium-, naproxen- and indomethacin-PHEMA ASD samples. A robust physical stability has also been demonstrated in indomethacin-PHEMA ASD by using polarized light microscopy to detect the onset of drug precipitation and no drug precipitation was observed for up to 8 months under direct exposure to an accelerated storage condition (40 °C/75% RH) for indomethacin loading levels below 16.7% *w/w*¹².

3.2. Swelling kinetics

The swelling property of crosslinked hydrogels is important not only to reach an adequate drug loading but also to regulate the rate of drug release. During drug release, the time evolution of the solvent penetrating front and normalized dimensional changes of drug-loaded PHEMA hydrogel beads is a function of crosslinking density, drug solubility and initial drug loading. For example, two moving boundaries (swelling front and drug dissolution front) were generally observed for poorly water-soluble diclofenac sodium in PHEMA hydrogels at a high drug loading range of 25%–30% *w/w* as the aqueous medium penetrates into the matrix, whereas a single fast-moving swelling front was observed below this range of drug loading⁴⁰. The dimensional changes of swelling PHEMA beads generally go through a maximum in radius followed by a gradual decrease to an equilibrium dimension during the drug release^{37,40}. Therefore, in PHEMA-based ASD systems, as the swelling phase progresses, the amorphous drug entrapped in the PHEMA hydrogel will be first converted into supersaturated solution and then released by diffusion into the dissolution medium. Meanwhile, the unreleased drug in the swollen matrix is still confined in the interstitial space between crosslinked polymer chains which can interact with the PHEMA polymeric network thereby inhibiting its rapid nucleation and crystallization in the hydrogel phase until the dissolved drug is released into the external medium in a more diluted form. The swelling behavior of hydrogels and the inhibition of drug nucleation and crystallization in the swollen gel phase are unique characteristics that are absent in conventional water-soluble and porous water-insoluble ASD carrier systems.

3.3. Diffusional drug release kinetics

The dissolution of ASD from insoluble crosslinked PHEMA hydrogels is regulated by a diffusion-controlled mechanism where the hydrogel matrix is insoluble and the dissolved amorphous drug (converting into highly supersaturated drug solution) slowly diffuses out of the hydrogel network. As a result, the degree of supersaturation in the dissolution medium generated by the PHEMA ASD system gradually increases. This gradual accumulation of drug concentration in the external medium reduces the driving force (*i.e.*, drug concentration difference between the hydrogel and the external medium) thus slowing the drug release from the hydrogel matrix. This feedback-controlled mechanism allows the avoidance of the critical supersaturation window above which spontaneous nucleation and crystallization will occur. As discussed in Section 3.2, entrapping the supersaturated drug solution in the swollen hydrogel phase can inhibit the nucleation and crystallization rates until the drug is released by diffusion from the hydrogel surface into the external medium in a more diluted form. On the other hand, ASDs based on water-soluble polymer carriers are generally dissolved quickly in the early stage of the

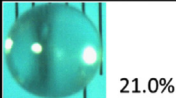
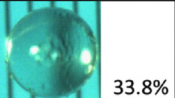
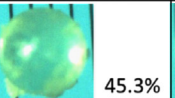
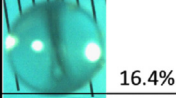
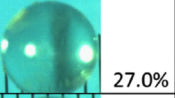
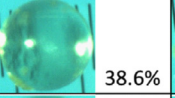
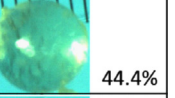
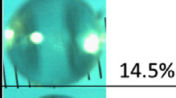
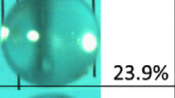
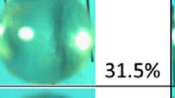
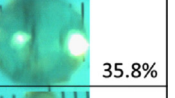
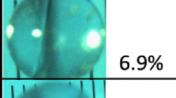
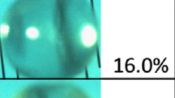
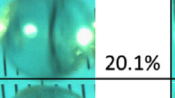
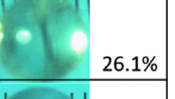
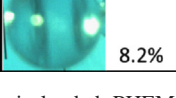


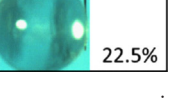
Loading solution conc. EGDMA conc. mol%	50 mg/mL	100 mg/mL	200 mg/mL	300 mg/mL
	0.66%	 21.0%	 33.8%	 45.3%
1 %	 16.4%	 27.0%	 38.6%	 44.4%
3 %	 14.5%	 23.9%	 31.5%	 35.8%
5 %	 6.9%	 16.0%	 20.1%	 26.1%
10 %	 8.2%	 13.7%	 16.6%	 22.5%

Figure 2 Characteristics of indomethacin-loaded PHEMA beads as a function of crosslinking agent concentration and loading solution concentration. Photographs of corresponding indomethacin-PHEMA samples on scale lines of a microscope slide (between scale lines: 100 μm) showing evidence of the threshold of drug loading levels. Figure adapted from reference 12 (reproduced with permission from the *European Journal of Pharmaceutics and Biopharmaceutics*, Copyright Elsevier 2012).

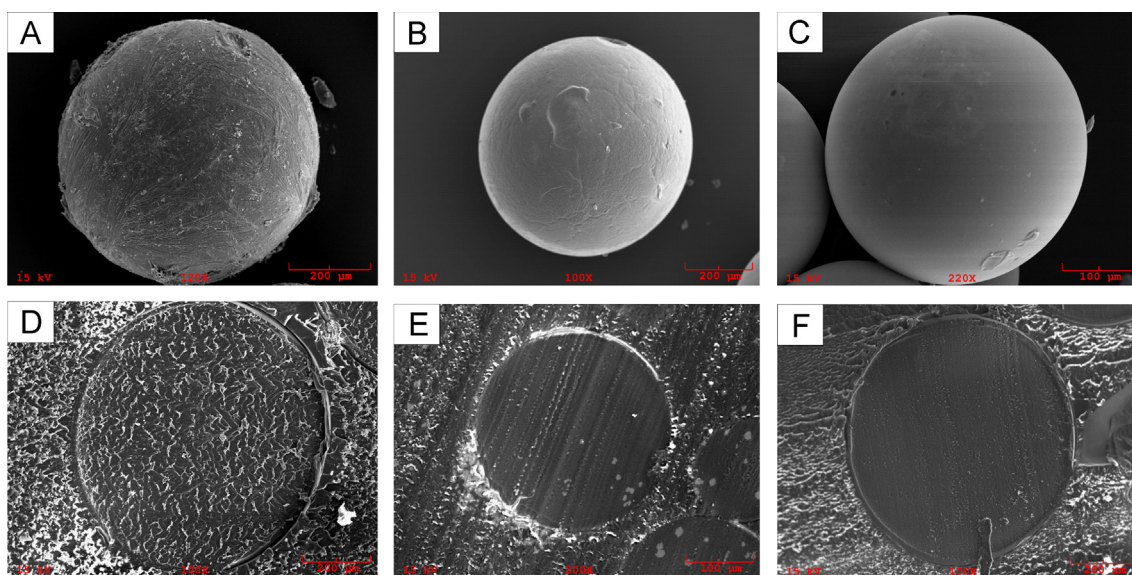


Figure 3 SEM images showing surface morphology (A–C) and cross section (D–F) of PHEMA beads (crosslinked with 0.66 mol% EDGMA) at different indomethacin loading levels: (A) 48.1% w/w, (B) 26.1% w/w, (C) 0% w/w, (D) 41.4% w/w, (E) 26.1% w/w and (F) 0% w/w. Images adapted from reference 12 (reproduced with permission from the *European Journal of Pharmaceutics and Biopharmaceutics*, Copyright Elsevier 2012).

dissolution process resulting in an initial surge of supersaturation followed by a decline in drug concentration due to the nucleation and crystallization events originated from the rapid buildup of supersaturation. However, such a decline in drug supersaturation can be delayed to different extents depending on the stabilizing effects of the dissolved polymer in the dissolution medium. Among various available water-soluble polymer carriers, hydroxypropyl methylcellulose acetate succinate (HPMCAS) has been identified as the most effective in achieving and maintaining drug

supersaturation when employed in ASDs^{42,43}. To provide a head-to-head comparison of solubility enhancement, the kinetic solubility profiles of indomethacin ASD in PHEMA, PVP (another commonly used hydrophilic polymer for ASD) and HPMCAS under nonsink dissolution conditions are presented in Fig. 4. A sink index (SI) defined as $SI = C_s V / (\text{Dose})$ is used here to characterize the extent of deviation from sink condition for the dissolution experiments of supersaturated ASD samples, where C_s is the solubility of crystalline drug, V the volume of dissolution

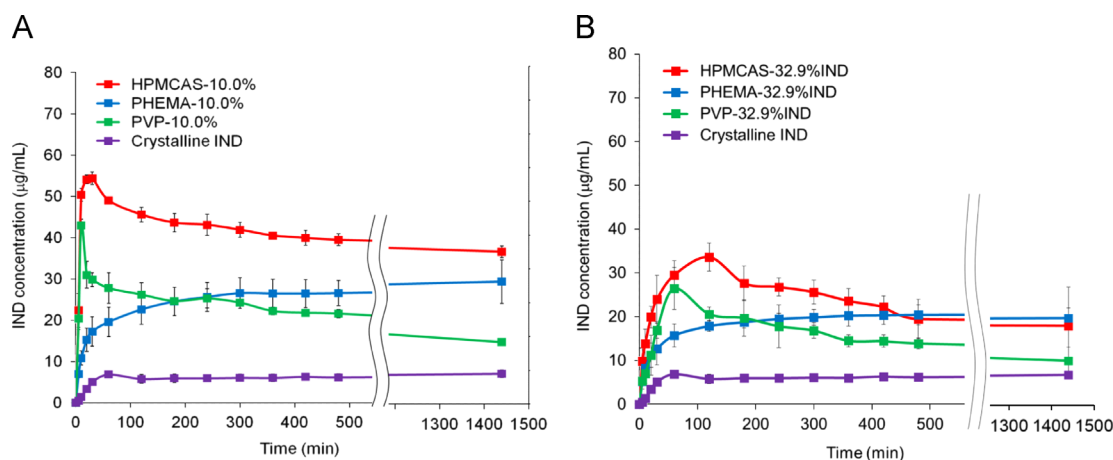


Figure 4 Comparison of IND dissolution profiles from ASD versus that of crystalline IND under nonsink dissolution condition ($SI=0.1$): (A) ASD with 10.0% *w/w* IND in PHEMA (average particle size 108 μm), PVP (63 μm) and HPMCAS (63 μm) and (B) ASD with 32.9% *w/w* IND in PHEMA (108 μm), PVP (63 μm), HPMCAS (63 μm). Figure adapted in part from reference 12 (reproduced with permission from the *European Journal of Pharmaceutics and Biopharmaceutics*, Copyright Elsevier 2012).

medium, and Dose the total amount of drug in the sample¹². A larger SI translates to a dissolution system that is closer to the sink condition (note: a perfect sink condition is achieved when $SI > 10$). It can be seen that the initial indomethacin solubility enhancement is higher for ASDs based on PVP and HPMCAS but the extent of solubility enhancement of indomethacin ASD in PHEMA falls between those in PVP and HPMCAS at 10.0% *w/w* drug loading after 6 h (Fig. 4A) and outperforms those in PVP and HPMCAS at 32.9% *w/w* drug loading after 8 h (Fig. 4B) under nonsink dissolution conditions ($SI=0.1$). It is worth noting that in this case the dissolution medium for the indomethacin-PHEMA ASD system remains supersaturated even after 24 h in the absence of any dissolved polymer which may inhibit crystallization. The apparent first-order drug dissolution from ASD indomethacin in PHEMA represents a balance of interrelated processes of diffusion-controlled drug release from the hydrogel matrix and recrystallization of supersaturated drug solution in the dissolution medium under nonsink dissolution conditions.

During the dissolution from PHEMA-based ASDs, the initial buildup of drug concentration in the external dissolution medium reduces the diffusional driving force for the drug to be further released from the matrix (*i.e.*, feedback-controlled mechanism), thus preventing the creation of excessively supersaturated drug solution in the dissolution medium thereby avoiding the critical supersaturation window above which spontaneous nucleation and crystallization will occur. When nuclei and crystallites start to form and consume dissolved drug molecules from the supersaturated dissolution medium, any reduction in drug concentration from such events will promote additional drug release from the matrix to maintain supersaturation for an extended period of time. Such coupled feedback-controlled balancing scheme will continue until no drug can be further released from the hydrogel matrix, beyond which drug concentration in the supersaturated dissolution medium will eventually decline due to continued nucleation and crystallization events. Therefore, ASD in hydrogels exhibits a completely different overall concentration–time curve than that based on soluble polymers primarily because the feedback-controlled diffusion mechanism avoids a sudden surge of supersaturation in the surrounding dissolution medium and thus prevents spontaneous and uncontrolled nucleation/crystallization.

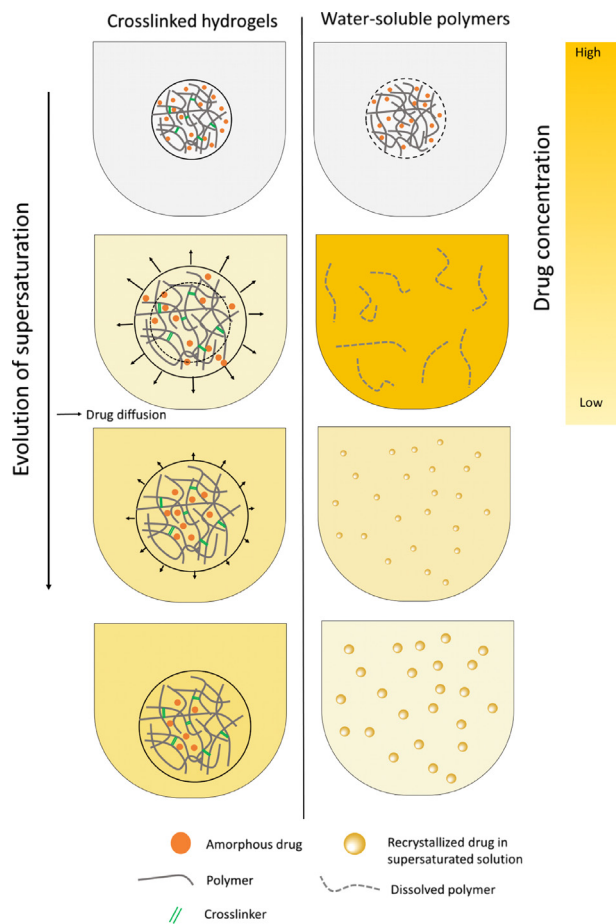


Figure 5 Amorphous drug release mechanism: crosslinked hydrogels vs. water-soluble polymers.

This enhancement of kinetic solubility profiles is evidently shown by the lack of any depreciation of drug concentration during the first 24 h of dissolution (Fig. 4) which contrasts the concentration decline normally encountered with ASDs based on water-soluble

carriers under nonsink dissolution conditions. An obvious corollary here is that other properly designed diffusion-controlled matrix ASD systems in principle should exhibit advantageous kinetic solubility profiles and maintenance of supersaturation similar to that of the present hydrogel ASD system. The strategy of employing diffusion-controlled drug release (whether short or extended term) will therefore provide the necessary feedback control to maintain supersaturation and avoid rapid nucleation and crystallization events in the dissolution medium under nonsink dissolution conditions.

To further illustrate the above described differences in drug release mechanism, Fig. 5 depicts the evolution of supersaturation of amorphous drugs released from crosslinked hydrogels versus that from water-soluble polymers. When used as immediate-release dosage forms, ASD based on water-soluble polymers tends to produce a highly supersaturated local environment upon dissolution of the polymer carrier, which often results in rapid recrystallization of the dissolved drug, thereby reducing the local drug concentration and the achievable supersaturation level of the solid dispersions. It is therefore not surprising that solid dispersions of poorly water-soluble drugs in water-soluble polymers usually experience rapid drug recrystallization from supersaturated drug solution upon dissolution of the water-soluble polymer carriers. Whereas the ASD in hydrogels avoids a sudden surge of supersaturation in the surrounding dissolution medium through the above described feedback-controlled diffusion mechanism and thus achieving a more sustained level of supersaturation than that based on water-soluble polymers. This further demonstrates the potential comparative advantage of designing an oral ASD dosage form based on crosslinked hydrogels.

3.4. Effect of rate of supersaturation generation

As discussed above, a sustained level of supersaturation can be achieved by gradual drug dissolution from ASD based on cross-linked PHEMA hydrogels, later surpassing that based on water-soluble polymer carriers as the drug concentration in the latter case declines due to more rapid de-supersaturation¹². Similar observations showing more sustained supersaturation resulting from a more gradual drug release under nonsink dissolution conditions have also been reported for drug release from swelling clay minerals⁴⁴ and ordered mesoporous silica materials¹⁴ in the absence of any crystallization inhibitor. In addition, Six et al.⁴⁵ have demonstrated that Sporanox[®], an ASD formulation of itraconazole in polymeric carrier HPMC having a slower *in vitro* dissolution rate than ASD prepared in Eudragit E100 and Eudragit E100/PVPVA64, actually produces a better oral bioavailability enhancement for itraconazole. In fact, fast dissolution of a supersaturating drug delivery system does not always translate to an optimal *in vivo* performance^{14,46}. These observations suggest that the rate of supersaturation generation may play an important role in determining the overall kinetic solubility profiles and the level of supersaturation achieved. Although the degree of supersaturation is well recognized as the driving force for the nucleation and crystallization processes, the effect of rate of supersaturation generation on the time evolution of the overall kinetic solubility profiles was not recognized and had not been explored prior to our work. We have recently shown for the first time that the rate of supersaturation generation plays an important role in determining the level of transient solubility enhancement, thereby affecting the overall kinetic solubility profiles in a dissolution medium free of

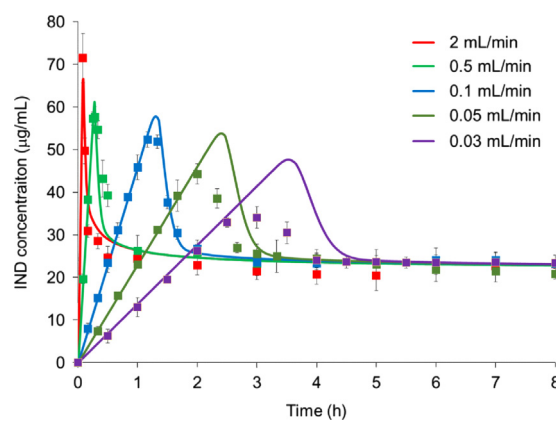


Figure 6 Comparison of kinetic solubility profiles of indomethacin between experimental and predicted results as a function of supersaturation rate generated with various drug solution (indomethacin in ethanol) infusion rates under nonsink dissolution condition ($SI=0.1$). Figure adapted in part from reference 47 (reproduced with permission from *Molecular Pharmaceutics*, Copyright American Chemical Society 2013).

any crystallization inhibition⁴⁷. We also proposed a comprehensive mechanistic model based on the classical nucleation theory taking into account both the particle growth and ripening processes to predict experimental kinetic solubility profiles under varying rates of supersaturation generation and recrystallization. This semi-quantitative analysis elucidates the dependency of the overall time-concentration profiles on the rate of supersaturation generation from the dissolution of non-equilibrium amorphous drugs. In the absence of any dissolved polymer or crystallization inhibitor, both of the experimental data and predicted results confirm that the faster rise of supersaturation will inevitably lead to an earlier but higher maximum kinetic solubility and a sharper decline in the de-supersaturation phase. Conversely, a slower rate of supersaturation generation results in a lower maximum kinetic solubility followed by a more gradual decline in drug concentration. These trends are clearly illustrated in Fig. 6 where experimental data at different rates of supersaturation generation (through drug infusion) are compared with simulated results based on our comprehensive mechanistic model⁴⁷. Given the fact that the mechanistic model simulation was based solely on physical parameters reported in the literature without employing any curve fitting, the agreement between the experimental data and model prediction can be considered as quite good. These trends are also consistent with our results on ASDs based on crosslinked PHEMA hydrogels as reported in Figs. 4 and 5 where a slower drug release from the hydrogel results in a lower but broader and more sustained drug supersaturation.

4. Safety assessment of hydrogel system for oral dosage form

Orally administered excipients must be stable, non-toxic, biocompatible in the GI tract and compatible to API and other excipients in the formulation in order to satisfy regulatory requirements. Full *in vivo* studies such as biodistribution, immune response, clearance and chronic toxicology studies for different durations are generally needed to demonstrate that new excipient is safe for usage in human drug products. The approval process of introducing a novel pharmaceutical excipient onto the market requires expensive

toxicological investigations and typically takes a similar period of time as that of a new API⁴⁸. Due to the complexity and high cost of long-term toxicological and clinical testing, PHEMA has not yet been used as an oral excipient in FDA approved drug products⁴⁹. Nevertheless, PHEMA hydrogel has a long history of human use as biomedical implants and for controlled drug release from medical devices such as contact lenses and wound dressings. A number of *in vivo* tests using PHEMA hydrogel delivery systems have produced favorable results in blood and tissue compatibility^{50–53}. Moreover, no toxic abnormalities were reported when crosslinked PHEMA hydrogels loaded with diclofenac sodium and theophylline were administered orally and rectally, respectively, to human subjects in clinical PK studies^{54,55}. Since crosslinked hydrogels for the oral delivery purpose are generally of micron sizes and insoluble in the GI fluid, cellular internalization or absorption through the mucosal membrane of the GI tract is very unlikely. Therefore, the above mentioned lines of evidence suggest that crosslinked PHEMA hydrogel beads would be an attractive candidate excipient for oral ASD drug products to enhance the solubility and bioavailability of poorly water-soluble drugs. To promote the practical application of PHEMA hydrogels as an excipient for oral ASD dosage forms, long-term oral toxicity studies should be investigated and safety established in the future.

5. Rate-controlled drug release from PHEMA Hydrogel

Controlled-release (CR) formulations have several potential advantages over immediate-release (IR) dosage forms, such as providing a more uniform and prolonged therapeutic effect to improve patient compliance, reducing the frequency of dosing, minimizing the number of side effects and reducing the strength of the required dose while increasing the effectiveness of the drug. CR-ASD formulations of poorly water-soluble drugs should comprise both functions of solubility enhancement and modulation of the rate of drug release. Unfortunately, complicated design of CR-ASD formulations often leads to poor reproducibility of physicochemical properties, difficulties in dosage form development, less feasible for scale-up manufacturing, and potential physical instability⁹. On the other hand, PHEMA hydrogel beads can easily achieve sustained release by adjusting appropriate particle size and chemical composition (*e.g.*, copolymerizing with hydrophobic monomers). Different from other complicated designs of CR-ASD formulations such as an osmotic pump system, PHEMA provides versatility of designing either IR or CR delivery systems for amorphous pharmaceuticals using the same hydrogel matrix. In addition to adjusting the drug release profiles of PHEMA hydrogels through co-polymerization with other monomers to affect the macromolecular relaxation process during the swelling phase^{56,59}, modulation of drug release from PHEMA hydrogels is also feasible by generating a non-uniform initial drug concentration distribution in the hydrogel matrix to accomplish a near constant-rate drug release^{57,58}.

6. Conclusions

Contrary to optimistic expectations from a large number of relevant previous studies, only a handful of marketed oral drug products have been derived from amorphous pharmaceuticals, in spite of a long history of research and publications since the early 1960s. At present, for instance, only Gris-PEG[®] (griseofulvin-PEG,

antifungal, Dorsey/Sandoz), Sporanox[®] capsules (itraconazole-HPMC, antifungal, Jessen Pharmaceutica), Cesamet[®] (nabilone-PVP, pain relief, Eli Lilly) and Kaletra[®] tablets (lopinavir/ritonavir in PVP-VA, Abbvie) are commercially available as immediate-release solid dispersion systems. Practically no controlled release oral products based on pharmaceutical solid dispersions have been commercially developed although many poorly water-soluble drugs would require additional release-rate modulation to enhance the duration and/or onset of action while minimizing drawbacks due to their short half-lives, gastric irritation potential or slow onset of action. Solid dispersion systems in PHEMA hydrogels would be ideal for achieving immediate release of amorphous drugs as well as a modulated release through appropriate selection of polymer composition and particle size for release rate control. Such hydrogel based ASDs are attractive because they can avoid a sudden surge of supersaturation during dissolution through a feedback-controlled diffusion mechanism and thus achieving a more sustained level of supersaturation than that based on conventional water-soluble polymers. This approach should bring hope for designing more versatile and more cost-effective oral dosage forms for potential drug candidates that have low aqueous solubility without resorting to the more complicated dosage design such as push-pull types of multi-layer osmotic pumps in tablet or capsule form. While the *in vitro* dissolution results of ASD based on PHEMA hydrogels show assuring applicability for oral drug delivery as a platform for both immediate- and controlled-release delivery of poorly water-soluble drugs, whether such solubility advantage can translate into *in vivo* bioavailability enhancement requires further confirmation. The current comparative research on solid molecular dispersions of amorphous pharmaceuticals in PHEMA hydrogels versus other carrier systems also contributes to the general scientific understanding on factors such as the rate of supersaturation generation, supersaturation level and crystallization kinetics on the overall kinetics solubility profiles generated by various supersaturating drug delivery systems.

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