The role of polymers in oral bioavailability enhancement; a review

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Abstract

One of the most important obstacles to successful oral drug delivery is the poor solubility of many drugs in aqueous media. This problem is of intense scientific and practical interest, impacting the effectiveness of marketed drugs, as well as the success rate and expense of new drug development. A number of solubility enhancing techniques have been developed over recent decades, including complexation with cyclodextrins, reducing particle size, forming lipid dispersions, and creating intimate mixtures of drug and polymer in the solid state (amorphous solid dispersion, or ASD). Polymers (and in the case of cyclodextrins, oligomers) are indispensable to each of these approaches. We describe in this review the design and function of polymers in each of these solubility enhancement methods, highlighting structure-property-function relationships, pointing out the advantages and disadvantages of each approach, and describing the functional demands upon current and future polymers. We conclude by discussing unresolved issues that may be addressed in the future by polymer scientists.

1

2

3 **Keywords:**

4 Cellulosic polymers

5 Amorphous solid dispersion

6 Aqueous solubility enhancement

7 Drug solubilization and stabilization

1

2 1. Scope

3

4 Polymers have been used in drug delivery for many decades, often performing
5 functions that are important but relatively routine, such as serving as bulking agents or as
6 materials intended to swell upon contact with gastrointestinal (GI) media, leading to drug
7 release. Our focus in this review is more narrow; we choose first of all to focus on oral
8 delivery, since it is the most widely used delivery route. We choose further to focus on
9 polymer roles in which the polymer is bringing specific functional benefit to the
10 formulation that is highly dependent on polymer design and structure. Finally, we choose
11 to focus further on one type of functional benefit, that of solubility enhancement, since
12 enhancement of drug solution concentration, and thereby oral bioavailability, is one of
13 the most challenging and important issues facing pharmaceutical and polymer scientists
14 today.

15 2. Oral drug delivery and impediments thereto

16

17 The majority of drugs are administered by the oral route; as tablets, capsules, or
18 solutions. Why is oral administration so often the method of choice for providers and
19 patients? Oral drug delivery is typically preferred vs., e.g., intravenous injection, in part
20 because it allows *administration* of precise doses, is inexpensive **since** administration
21 usually can be done by the patient, and is generally comfortable for patients, leading to
22 relatively high patient adherence to dosage regimes. Due to its large surface area, the
23 small intestine is the primary absorptive organ for drugs in the human body. Although
24 stomach-specific drug delivery is desired in some cases (for example, floating beads
25 containing clarithromycin were designed to be delivered to the stomach site against
26 *Helicobacter pylori*) [1], many drugs are degraded in gastric media where the pH may be
27 2 or less, depending on patient age, health, diet, **fed/fasted state**, and potentially on other
28 drugs being taken by the patient. Meanwhile some drugs, such as aspirin and ibuprofen,
29 can cause severe stomach irritation if they are not protected from release in the gastric

environment (usually by enteric polymer coatings) [2-4]. Cellulose derivatives that are responsive to pH (enteric polymers) like cellulose acetate phthalate were among the first polymers to be used in drug delivery, resisting dissolution and thereby providing protection against strong acid and digestive enzymes in the stomach, then swelling and/or dissolving in the close to neutral pH environment of the small intestine to allow the drug to dissolve and permeate through the GI epithelium into the bloodstream. Other factors such as fed vs. fasted state, efflux transporters like P-glycoprotein, and metabolism in the enterocytes and in the liver also may have significant impact on oral drug delivery. For successful drug therapy, formulation scientists have to control solubility, permeability, metabolism and efflux transport of the pharmaceutical active using advanced formulation techniques [5].

However, efficient absorption of an orally administered drug is often difficult to achieve because of poor aqueous solubility. Modern drug discovery frequently involves screening of potential actives for strongest binding to an active site in an enzyme target, which is often a hydrophobic pocket; thus the candidate chosen in part due to binding strength is often hydrophobic. Refinement of drug structure to produce advanced candidates often produces highly crystalline compounds, since recrystallization is a convenient method for achieving high levels of drug purity, as well as physical and chemical stability. Crystallinity and hydrophobicity are both serious impediments to high aqueous solubility; inadvertent formation of a more thermodynamically stable crystalline phase of the active during storage can further reduce solubility and cause unacceptable variability [6]. The Biopharmaceutics Classification System (BCS) is used to classify drugs on the basis of their aqueous solubility and ability to permeate through the GI enterocytes. The magnitude of the solubility problem is illustrated by the fact that a high proportion of new and existing drugs and drug candidates, estimated to be as high as 80–90%, is classified as Class II (high permeability, low solubility) or Class IV (low permeability, low solubility) [7]. Conversion of drugs to more soluble salts is an historical method for enhancing aqueous solubility that does not necessarily involve polymers, often by making salts of drug amine groups with protic acids containing particular counter-anions [8]. This is often not a successful approach; for example, the

drug may lack an amine or other appropriate moiety for salt formation, or may not be stable under salt formation conditions. Frequently drug salts are less chemically stable, and the salt forms do not always serve the purpose of **adequately** enhancing solubility and bioavailability. Moreover, reversion to the original free acid or base form may also take place during dissolution [8]. As a result, solubilization of drugs by salt formation is frequently unsuccessful, and other alternatives are necessary.

3. Polymer Approaches for Solubility and Bioavailability Enhancement

Scientists have frequently turned in recent years to polymers and oligomers to enable creation of systems that can overcome aqueous solubility limitations and achieve effective oral drug delivery. Some of these approaches have provided added benefits, including targeted release [9], or precise control of release rates such as release that is zero-order with respect to time, enabling much more constant plasma drug levels [10, 11]. These useful properties help to achieve enhanced patient convenience and compliance with lower dosage and frequency of medication, and in the case of drugs with narrow therapeutic indices, may significantly reduce side effects. In the following sections, we describe several key polymer- and oligomer-based approaches to solubility enhancement.

3.1 Cyclodextrin-drug complexation

Cyclodextrins (CDs) have been developed over the last several decades as effective delivery vehicles for achieving higher thermodynamic solubility of drugs via complexation [12]. Strictly speaking cyclodextrins are oligomers rather than polymers, but given their repeating poly(glucose) nature we felt it appropriate to include them in this discussion. Cyclodextrins are formed by enzymatic conversion of starch (mostly amylose) to cyclic oligomers of 6 (α), 7 (β), or 8 (γ) α -(1 $\rightarrow$ 4) linked glucose units. Topologically, the CD is a torus that has a hydrophobic interior and hydrophilic exterior edges. This structure allows the CD to host hydrophobic guest drug actives (often the host to guest molar ratio is 1:1) as inclusion complexes, which are typically water-soluble due to the hydrophilic edges of the torus; thus complexes with CDs are widely used in

1 pharmaceutical formulations to improve solubility of lipophilic drugs [13]. Complex
2 formation often involves addition of the drug to an aqueous CD solution, spontaneously
3 forming the soluble CD complex. Then the solid complex can be isolated from the
4 solution by methods such as co-precipitation or spray-drying. Solid complexes so
5 obtained can be easily reconstituted as solutions by adding water or saline for intravenous
6 administration. The major product of enzymatic synthesis from starch is β -CD (cyclic
7 heptamer), which is therefore most efficiently produced and has generally broad binding
8 affinity for hydrophobic drug solutes [14]. For these reasons β -CDs are the most widely
9 used for preparation of CD-drug complexes. However, β -CD is favorably oriented to
10 form intramolecular hydrogen bonds, resulting in a rather rigid, crystalline structure [15].
11 Therefore, β -CD has the poorest water solubility (1.85 g/100 mL, 25°C) of the native CDs,
12 and this negatively impacts complex solubility. **Because of this limited aqueous solubility,**
13 **injected β -CD can be problematic when it reaches the kidneys for excretion. It is prone to**
14 **crystallizing within kidney microtubules since water permeates through the microtubules**
15 **more rapidly than does β -CD, thereby concentrating the aqueous β -CD solution [16]. The**
16 **β -CD** crystals cause microtubule necrosis, potentially resulting in severe injury to the
17 kidneys. Due to these disadvantages, β -CD use in IV applications is not advisable and β -
18 CD only finds use in certain oral formulations.

19
20 To overcome this inherent low β -CD water solubility, researchers have
21 synthesized more soluble derivatives. Solubility is enhanced upon etherification through
22 disruption of the regular CD structure, thereby impairing crystal formation. Methylation
23 of β -CD to form methyl- β -CD (degree of substitution DS $\sim$ 10.5 – 15; **maximum possible**
24 **DS 21**) provided good water solubility (50 mg/mL). The fact that addition of a
25 hydrophobic substituent greatly increased water solubility highlights the importance of
26 crystallinity to CD solubility. Methyl- β -CD at first showed potential as a stable, simple
27 drug complexation agent [17]; however, this potential was clouded by the discovery by
28 Rodal et al. [18] that methyl- β -CDs may extract cholesterol from membranes. This
29 undesired impact on membranes may adversely impact the *in vivo* performance of
30 methyl- β -CDs. Ultimately, the concept of improving β -CD performance by modification
31 with hydrophilic substituents was proven. Important commercial examples include 2-

hydropropyl- β -cyclodextrin (HPCD) and sulfobutyl- β -cyclodextrin (SBCD) (**Fig. 1**). Both of these β -CD ethers are highly soluble (ca. 600 mg/mL solubility in water) and are used in multiple commercial intravenous drug formulations.

Figure 1. Syntheses of HPCD and SBCD

The anti-psychotic drug ziprasidone is a good example of the ability of SBCD to form more soluble drug complexes and enhance bioavailability. Ziprasidone is poorly soluble as its free base (ca. 300 ng/mL), and even its mesylate salt has aqueous solubility (0.89 mg/mL, pH 2.7) that is well below the stated formulation target of 20-40 mg/mL. It was reasoned that the salt form could not be fully dissociated to its soluble ionic product

1 in a physiologically acceptable aqueous solution. A strategy that combined SBCD with a
2 ziprasidone salt was developed to address the problem. Kim et al. prepared an 1:1
3 stoichiometric inclusion complex of ziprasidone mesylate (ZM) with SBCD (DS ~ 6.5),
4 which increased aqueous solubility to 44.0 mg/mL of ziprasidone, meeting the
5 formulation target [19]. Interestingly, the drug molecule is complexed as an intact ion-pair,
6 owing to the fact that the hydrophobic nature of the cyclodextrin cavity results in
7 interaction primarily with non-ionic molecules. A similar combination method of
8 ionization and SBCD complexation enhanced the aqueous solubility of kynostatin, a
9 tripeptide HIV protease inhibitor, substantially from its inherent solubility (4 µg/mL).
10 Optimal results (5-50 mg/mL) were obtained with high concentrations of SBCD (DS ~ 4,
11 50 wt%) at low pH (3.0) [20].
12

13 Complexation with HPCD is also an effective method for drug solubility
14 enhancement. HPCD's low cytotoxicity, minor organ irritation and weak haemolytic
15 activity [21] have permitted application in marketed pharmaceutical formulations.
16 Cyclodextrin complexation can also enhance chemical stability; for example, formation
17 of a stable HPCD (molar substitution (MS) 4.3)-rutin complex led to inhibition of
18 chemical or enzyme-catalyzed hydrolysis of the anti-oxidant, and enhanced GI stability in
19 an *in vivo* absorption study [22]. Boudad et al. also described a combined method of
20 HPCD (MS ~ 3) complexation and poly(alkylcyanoacrylate) nanoparticle incorporation
21 with saquinavir, a HIV protease inhibitor [23]. This formulation not only enhanced
22 saquinavir apparent solubility 400-fold at pH 7.0, but also achieved a 20-fold increase in
23 saquinavir loading compared to nanoparticles prepared in the absence of modified
24 cyclodextrins.
25

26 These dynamic CD-drug complexes (rapid equilibrium between complexed and
27 dissolved drug) are clearly useful in IV formulations to keep the drug soluble prior to
28 administration, and during the brief distribution phase post-administration. There was,
29 however, skepticism about whether they would be effective at keeping drugs soluble in
30 the GI tract *in vivo*, and thereby actually enhance drug oral bioavailability. Buchanan and
31 co-workers explored this question. They discovered that a new modified CD,

1 hydroxybutenyl- β -cyclodextrin (HBen β CD), is highly soluble in water and organic
2 solvents and forms complexes with a broad range of drugs [24]. HBen β CD was prepared
3 by reacting the parent β -CD with 3,4-epoxy-1-butene in the presence of potassium
4 hydroxide at elevated temperature. Low molecular weight by-products could be easily
5 removed by nanofiltration of the product; this is important since the presence of residual
6 β -CD must be avoided due to its aforementioned nephrotoxicity. From the MALDI-TOF-
7 MS analysis, HBen β CD was identified to have a random substitution pattern which
8 impeded crystallization and promoted rapid dissolution in water to afford high
9 concentrations (> 500 mg/mL) and good solubility in certain organic solvents as well (>
10 400 mg/mL in polyethylene glycol).

11
12 Studies of HBen β CD (MS 4.7) for enhancing *in vitro* solubility and *in vivo* oral
13 bioavailability have addressed the question of whether cyclodextrins can be useful in oral
14 formulations. Buchanan et al. examined oral administration of tamoxifen-HBen β CD
15 complex formulations [25-27]. These workers showed strongly enhanced solubility *in*
16 *vitro* at pH 6.8 (small intestine pH), and *in vivo* experiments in rats showed that these
17 formulations provided a 10- to 14-fold increase in bioavailability relative to that of
18 tamoxifen base alone, eliminating the need for conversion to tamoxifen nitrate salt to
19 enable higher solubility and efficacy. In other studies, complexes of HBen β CD with
20 saquinavir (~10 wt% incorporation by UV), which has poor aqueous solubility (207 ± 5
21 $\mu\text{g/mL}$ in base form and 2.1 ± 0.3 mg/mL in mesylate form), were discovered to enhance
22 equilibrium solubility by 26- and 6-fold, respectively. The dissolution profiles showed
23 that the complexes rapidly dissolve to form solutions that are stable with regard to
24 recrystallization in the pH range of 1.2-6.8 [28]. From the pharmacokinetic perspective,
25 three important parameters were measured; area under the plasma concentration-time
26 curves (AUC), maximum plasma drug concentrations (C_{max}), and time to reach C_{max} (T_{max})
27 [29]. The measured oral bioavailability (F) in rats after dosing with saquinavir mesylate
28 capsules is only 2.0 ± 0.7 %; oral administration of saquinavir base-HBen β CD complex
29 in capsules afforded a nearly 9-fold increase in oral bioavailability. This series of studies
30 proved that complexation with HBen β CD may provide benefit to drug delivery, for both

oral and IV formulations, and may be a valuable tool for increasing drug oral bioavailability. This evidence implies that the dynamic drug-cyclodextrin complexes can continue to solubilize the drug through the absorptive zone of the GI tract and present soluble drug to the epithelium for absorption into the bloodstream. The utility of complexation of drugs with properly designed CDs for oral bioavailability enhancement is clear, although it is limited by the necessity for drugs of the proper size, geometry and intrinsic solubility properties for CD complexation [30]. As will be discussed later, another potential drawback is that this method works by enhancing thermodynamic solubility via complex formation, and so does not increase the chemical potential difference for the drug across the membrane. As we will see, other polymer-facilitated solubilization methods can positively impact both solution concentration and permeability of drugs.

3.2 Nanosizing: Nanoparticles with large surface area

As drug particle size is decreased, the ratio of surface area to volume increases. Such reduction of drug particle size enables drugs to be dissolved more rapidly due at least in part to this increase in surface area, and for < 100 nm species, an increase in solubility. This approach, termed “nano-sizing”, has been used to formulate poorly-soluble drugs as nanometer-sized drug particles for better bioavailability, including in commercial formulations [31]. Frequently, co-grinding of poorly-soluble drug with polymeric stabilizer and surfactant is used to produce such nanoparticles [32]. The use of polymeric stabilizers such as cellulosics, polysorbates, or polyvinylpyrrolidones (PVP) is often necessary to inhibit hydrophobic aggregation of drug nanocrystals, by strong stabilizer absorption to the particle surface. The amount of stabilizer added during formulation is crucial because agglomeration or Ostwald ripening can occur at either too low or too high a drug to stabilizer weight ratio. It is important to recognize that, depending on the duration and intensity of the grinding process, the degree of crystallinity of the drug can also be reduced. To the degree that amorphous drug is created, supersaturation may occur upon nanoparticle dissolution, providing further bioavailability advantage (discussed in more detail in the section on amorphous solid

dispersions (3.5)).

Itoh et al. demonstrated a method of dry co-grinding poorly water-soluble drugs with PVP and sodium dodecyl sulfate (SDS) by means of a vibrational rod mill [33]. Absorption of negatively charged SDS on the particle surface created electrostatic repulsion. This repulsion retards agglomeration, affording good particle size stability in aqueous dispersions. Nonetheless, dry co-grinding is generally less effective than wet methods at reducing particle size, though the dry method may be preferred for drugs prone to hydrolysis. Liversidge et al. reported a wet milling method, termed “NanoCrystal® Technology”, for preparing nano-sized drug crystals [32]. Micron-sized drug crystals were subjected to media milling in a water-based dispersion, forming a homogeneous dispersion with mean nanoparticle diameters < 200 nm. Proprietary highly crosslinked polystyrene resin was frequently the milling medium and the entire process could be completed within 60 min. Takatsuka et al. further reduced the time of wet milling process to 5 min using a rotation/revolution mixer and zirconia balls [34]. The original macroparticulate drugs were dispersed in aqueous methylcellulose (stabilizer) solution, pulverized, and then freeze-dried for size analysis. Phenytoin nanoparticles were created with mean diameter of 129 nm, which was ~1/10 the diameter of the original drug. However the pulverized nanoparticles remained crystalline and crystallites could grow and aggregate over time during storage. Polymer characteristics including molecular weight, functional groups and charge, surface hydrophobicity, and surface energy difference between the drug and polymer can exert significant influence on preventing aggregation, with the exact relationships still being unknown. Hence, the choice of polymeric stabilizer often is largely empirical [35, 36].

Nanoprecipitation is a simple and efficient method for small-scale laboratory production of nanoparticles; dialysis and rapid precipitation techniques have been frequently employed. Membrane-dialysis of a compound dissolved in a solvent against a non-solvent yields regular nanospheres, whereas precipitation in a non-solvent by dropwise addition affords nanoscale bean-shaped particles [37]. A flash nanoprecipitation technique was invented by Prud’homme et al., in which a multi-inlet vortex mixer

(MIVM) was used to rapidly mix two or more streams, usually a drug solution and a polymer stabilizer solution (or a premixed drug-polymer solution [38]) mixing with one or more anti-solvent streams, to create high and uniform supersaturation [39]. The amphiphilic polymer was absorbed uniformly onto drug nanoparticle surfaces and this slowed down nanoparticle aggregation or growth. As a result, this method frequently resulted in production of nanospheres with **controllable and narrow size distribution**.

By applying nanosizing methodology, it was possible to form near-spherical-shaped nanoparticles that had average diameter of 200 nm, a 50-fold decrease from the original particle size, leading to an increase in surface area to volume ratio of nearly 50 fold [32]. The significant particle size reduction can lead to faster absorption and enhanced bioavailability. For example, nanosized particles of cilostazol (antiplatelet agent) with median diameter of 220 nm displayed a dramatic 5100 fold increase in dissolution rate in water vs. particles from hammer-milling, with a **median** diameter of 13 μm [40]. However, the 220 nm particles provided an extent of dissolution similar to or even lower than that observed for the unprocessed crystalline form [41], possibly due to the formation of aggregates, and/or because of poor observed wettability (nanoparticles floating on the surface of the dissolution medium) . A potentially general disadvantage of nanosizing is the possibility of contamination due to attrition of the grinding medium during nanoparticle preparation [42].

3.3 Lipid-based delivery

It has long been realized that oral bioavailability can be enhanced when a hydrophobic drug is co-administered with a fat-rich meal, due to solubilization or dispersion of the drug by the fats. Presentation of the poorly water-soluble drug as a solubilized formulation is the primary mechanism for lipid-based enhanced delivery [43]. By selecting the optimum lipid vehicle and form, it is possible to minimize or even eliminate crystallization of the drug in the GI tract. **The lipid component** can be non-digestible, including mineral oil, sucrose polyesters, or it can be digestible, including triglycerides (TG), diglycerides (DG), phospholipids (PL), fatty acids (FA), cholesterol

1 and other synthetic derivatives. Moreover, lipid-based delivery systems can be
2 formulated as solutions, suspensions, emulsions, microemulsions, or self-emulsifying
3 drug delivery systems [44]. Polymers frequently play important roles in creating these
4 lipid-based emulsions.

5
6 Traditional formulations of lipophilic drugs for lipid-based delivery are
7 straightforward. Drugs are dissolved or suspended in either a single lipid or a blend of
8 lipids, or incorporated into the oil phase of oil-in-water emulsions [45]. The chemical
9 nature of the lipid used can greatly impact the oral bioavailability of drugs after
10 administration. The important factors include fatty acid chain length, the degree of
11 unsaturation and the lipid class (TG, DG, PL or FA). For instance, for highly lipophilic
12 drugs such as cyclosporin [46] and halofantrine [47], a long chain triglyceride solution
13 formulation showed increased solubilization capacity, as well as more effective
14 lymphatic drug transport when compared with medium chain triglyceride solutions. In
15 most cases, surfactants and co-solvents are present in lipid-based formulation to aid the
16 solubility and they are polymeric, including polysorbates (Tween) and polyoxyl castor
17 oils (Kolliphor[®]) [48].

18
19 As the technology has been developed, self-emulsifying drug delivery systems
20 (SED DS) have been increasingly employed in oral administration. In a SED DS, a
21 mixture of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-
22 solvents spontaneously emulsifies in the GI tract and forms an oil-in-water emulsion or
23 microemulsion. Rapid emulsification generates a high surface area of interaction between
24 GI fluids and the drug-lipid formulation, which leads to enhanced drug dissolution and
25 absorption. The other advantage is that for lipophilic drugs with intermediate partition
26 coefficients ($\log P = 2-4$), SED DS result in increased drug loading capacity when
27 compared with other lipid formulations [49]. This increase is attributed to the fact that
28 those specific drugs are less soluble in lipids but much more soluble in amphiphilic
29 surfactants and co-solvents. Kim et al. compared the bioavailability of indomethacin
30 after oral administration of a SED DS (comprising 30% Tween 85 and 70% ethyl oleate)
31 vs. an indomethacin suspension [50]. The SED DS formulation showed a significant 57%

1 increase in AUC_{0-12h} vs. the indomethacin suspension after oral administration to rats.

2
3 **Figure 3.** Lipid digestion models for *in vitro* assessment of lipid-based formulations,
4 reprinted with permission from Ref. [44]; Copyright 2008 Elsevier.

5
6 An important limitation of lipid-based delivery systems is a lack of
7 comprehensive knowledge of the formulation parameters that can be accurately
8 predictive of *in vivo* performance for lipophilic drug candidates. Therefore, only a few
9 human *in vivo* studies have been reported in the literature. Recently, valuable information
10 has been provided by an *in vitro* lipolysis simulation model (**Fig. 2**). This may enhance
11 predictive power and thereby help move lipid-based systems towards more widespread
12 commercial development.

14 3.4 Micellar solubilization – The use of artificial surfactants as excipients

15

1 The use of surface-active agents as excipients has been a common approach to
2 improve the apparent aqueous solubility of lipophilic drugs. Common monomeric
3 surfactants include sodium dodecyl sulfate, dodecyltrimethylammonium bromide,
4 polysorbates, polyoxyethylated glycerides and mono- and di-fatty acid esters of low
5 molecular weight polyethylene glycols [51]. They are generally composed of a
6 hydrophilic (polar) head moiety and a hydrophobic (nonpolar) tail moiety. Above the
7 critical micelle concentration (CMC, which is in the range of 0.05-0.1% for most
8 surfactants), the hydrophobic tails assemble to the interior to avoid contact with water,
9 and the head groups stay on the outside interacting with water. Therefore, surfactants can
10 incorporate lipophilic drugs into micelles, which can lead to extraordinary increases in
11 apparent solubility [52]. The effectiveness of surfactants in micellar solubilization of
12 drugs depends on several factors as described below.

13 1. Drug solubility is enhanced with increasing temperature [53]. It was
14 reasoned that thermal agitation led to increasing micellar volume, in addition to
15 the increase in drug solubility with elevated temperature.

16 2. Increased ionic strength usually gives rise to solubility enhancement,
17 especially in the presence of ionic surfactants. The addition of salt decreases the
18 repulsion between like-charged groups, thereby increasing the aggregation
19 number and free volume of the micelles. Hydrophobic drugs are preferentially
20 solubilized in the micelle core [54].

21 3. Solution pH also affects the extent of drug solubility, depending on the
22 chemical nature of the drug. As discussed previously, pH adjustment may change
23 the equilibrium between ionized and un-ionized forms of some drugs [55, 56].
24

25 Recently, polymeric micelles for drug solubilization have gained increased
26 attention. They are derived from block co-polymers consisting of a hydrophobic core
27 (such as polypropylene oxide) and a hydrophilic shell (such as polyethylene oxide). Well-
28 designed polymeric micelles exhibit better solubilization capacity than conventional
29 surfactant micelles, mostly thanks to higher number and larger cores of micelles formed
30 [57]. The Kataoka and Kabanov groups have led the development of polymeric micelles.
31 The aqueous solubility of free doxorubicin (an anticancer drug, DOX) is less than 50

1 $\mu\text{g/mL}$. Kataoka et al. prepared and studied PEO-*b*-poly(L-aspartic acid)-DOX
2 conjugates. PEO-poly(aspartic acid)-DOX was able to form micellar structures with a
3 diameter of ~ 50 nm and a narrow size distribution in phosphate-buffered saline [58]. The
4 micellar conjugates suppressed growth of C26 murine tumor cells to an extent three times
5 greater than that achieved by injecting the same amount of free DOX, and prolonged the
6 life spans of all treated mice [59]. Kabanov et al. investigated the antitumor effects of
7 DOX formulated with PEO-PPO-PEO block co-polymers (Pluronic[®]) [60]. Pluronic[®]
8 copolymers are synthesized by sequential anionic polymerization of propylene oxide and
9 ethylene oxide monomers. After optimizing the ratio between hydrophobic and
10 hydrophilic segments, treatment with these micelles considerably extended the lifespan of
11 the mice ($> 150\%$) and inhibited tumor growth ($> 90\%$), when compared with animals
12 treated with free drug.

13
14 In another example, biodegradable polymeric micelles made of PEO-*b*-poly(D,L-
15 lactic acid-*co*-caprolactone) were utilized to incorporate paclitaxel [61], an important
16 antitumor drug with aqueous solubility of only $1 \mu\text{g/mL}$. After administration, the
17 polymeric micellar paclitaxel formulation produced a 5-fold increase in the maximum
18 tolerated dose compared with the commercial formulation containing Kolliphor[®] EL.
19 Micellar paclitaxel-treated animals showed an increased survival time, and long-term
20 survivors (20% of those tested) were present only in the polymeric micelle formulation
21 group.

22
23 One drawback of micellar solubilization for oral administration of BCS class II
24 drugs is that confinement of the drug within the micelle can significantly decrease the
25 free fraction of drug, resulting in decreased intestinal membrane permeation [62, 63].
26 Given the limited time (ca. 6 h) that oral formulations spend in the primary absorptive
27 zone of the GI tract (stomach and small intestine), this can be a significant impediment to
28 bioavailability. Furthermore, barriers to use of polymeric micelles such as low drug
29 loading efficiency, poor stability after administration, and difficulty in transporting
30 through membranes are still to be resolved, in order to consistently and predictably reach
31 desired bioavailability [64].

3.5 Amorphous solid dispersions

It has been discovered that poor solubility often can be successfully overcome by formulation of drugs as amorphous solid dispersions (ASD) in polymer matrices [6], and in recent years this methodology has received strongly increased attention, including in commercial applications. When entrapped in a high energy, metastable amorphous form, drug molecules do not have to overcome the crystal **lattice energy** in order to dissolve. **Studies have** revealed that intimate mixing of drug with a compatible polymer leads to the formation of a molecular dispersion, disrupting the drug crystal lattice, which increases the rate and extent of drug dissolution, thereby frequently enhancing its oral bioavailability [65]. In addition, enhanced drug solubility enabled by ASD relies on formation of metastable supersaturated solutions rather than on increases in drug thermodynamic solubility [66]. As a result, recent publications have shown that the supersaturated solutions generated by these ASD formulations enhance drug transport across the GI epithelial membrane, while other formulation methods including cyclodextrin complexation, micellar solubilization or co-solvent addition, all of which work by enhancing thermodynamic solubility, improved solubility but not membrane transport rate [5, 62, 63, 67, 68].

Several review papers have discussed ASD formulation processes, which can be classified into two categories: melt and solution methods [69]. In the hot melt extrusion (HME) process, the drug and the carrier must be miscible in molten form. After extrusion, the drug/polymer melt can be cooled and shaped into tablets, pellets, granules or milled into a powder. Polyvinylpyrrolidone copolymer (co-povidone), hydroxypropylmethyl cellulose and other thermally processable polymers have been used for the production of ASDs with a wide range of pharmaceutical ingredients [70]. However, one limitation of melt processing is that the drug and the polymer should both be thermally stable against degradation and chemical reactions at melt processing temperature, including stability against reactions with one another. This also suggests that the processing window must be wide enough for thermal extrusion of solid dispersions. Therefore, preparing ASDs by

solution methods offers more flexibility with regard to polymer and drug properties. For small scale pre-screening, solvent evaporation is widely used. As a standard procedure, the drug and the polymer are dissolved in a common solvent and then the solvent is removed by spin-coating, rotary evaporation under reduced pressure, or dialysis followed by lyophilization. Co-precipitation can also be utilized to prepare ASDs, by dissolving polymer and drug in a common solvent, then adding to a common non-solvent to co-precipitate drug and polymer. For industrial scale ASD preparation, spray-drying (SD) is most commonly used, producing a powder by rapid drying with a moderately heated nitrogen gas stream. A scheme of spray-drying and the image of a Mini Spray Dryer B-290 are shown in **Fig. 3**. This mild process may be applied to a broad range of drug candidates and is flexible with regard to scale — ranging from tens of milligrams to metric tons.

Figure 3. Spray-drying process and the image of a Mini Spray Dryer B-290, reprinted from Ref. [71]; Open access 2012 InTech.

4. Polymer Matrices for ASD Formulation

ASD performance depends upon the polymeric matrix and its interactions with

1 the drug, especially when the incorporated drug is a fast crystallizer. Therefore, polymer
2 design and selection are crucial. First and most obvious, the polymer must be benign in
3 the GI tract. The polymer and any predictable products of *in vivo* chemical or enzymatic
4 breakdown should be non-toxic, ideally endogenous or dietary. In most cases, exposure to
5 the polymer will be limited to the GI tract since by Lipinski's rules most polymers will
6 not passively permeate from the GI tract into the bloodstream [72]; one exception could
7 be exposure to nanoparticle formulations [73]. In addition, it is essential that the polymer
8 should have the capability of forming a molecular dispersion with the drug. Specific
9 interactions between polymer and drug (e.g. hydrogen bonds) are needed to aid
10 miscibility and avoid phase separation [74]. One potential disadvantage of ASDs is that
11 due to entrapment of the drug in a high-energy state, the metastable amorphous drug may
12 crystallize over time. Even trace amounts of crystallinity in the solid dispersions can seed
13 rapid crystal growth, diminishing effectiveness, increasing variability, and shortening the
14 shelf-life of the dosage form. The glassy state can severely restrict drug molecular
15 mobility thereby retarding crystallization, thus high polymer glass transition temperature
16 (ideally $T_g \geq 50^\circ\text{C}$ above any likely ambient temperature, to compensate for the potential
17 plasticizing effect of the drug and likely plasticizing effect of ambient moisture) is an
18 important criterion [75]. Additionally, since ASDs generate supersaturated solutions from
19 which the drug has an inherent propensity to crystallize, polymers must have the ability
20 to stabilize the drug against crystallization from supersaturated solutions over the relevant
21 GI tract residence time ($\geq$ ca. 6 h).

22

Ivacaftor, Cystic Fibrosis
(HPMCAS, SD)

Lopinavir, HIV
(PVP-VA, HME)

Ritonavir, HIV
(PVP-VA, HME)

Vemurafenib, Cancer
(HPMCAS, precip.)

Telaprevir, HCV
(HPMCAS, SD)

Tacrolimus, immunosuppressant
(HPMC, SD)

Everolimus, immunosuppressant
(HPMC, SD)

Etravirine, HIV
(HPMC, SD)

Itraconazole, antifungal
(HPMC, SD, HME)

Figure 4. Marketed ASD formulations (drug, indication, polymer (HPMC is hydroxypropyl methyl cellulose; HPMCAS is hydroxypropyl methyl cellulose acetate succinate; PVP-VA is poly(vinyl pyrrolidinone-*co*-vinyl acetate)), and processing method (SD is spray-drying; HME is hot-melt extrusion))

These issues have been dealt with successfully through application of polymer science, so much so that many polymer-based ASD drug formulations have now been marketed (**Fig. 4**) and many more are in the approval pipeline. We will discuss the utility and structure-property relationships of specific polymer types in ensuing sections.

4.1 Synthetic polymers

4.1.1 Hydrophilic polymers: **poly(vinyl pyrrolidone)** (PVP), poly(ethylene glycol) (PEG)

PVP and PEG have often been used to prepare ASDs. These water-soluble synthetic polymers, in particular PVP, are commonly used to stabilize the amorphous

1 drug state during storage [76]. PVP has a relatively high T_g (177°C). High polymer T_g .
2 affords higher formulation T_g , as can be predicted using the Couchman-Karas equation
3 [6], thus prolonging formulation shelf-life. Polymer T_g is not the only contributor to
4 stabilization against drug crystallization from the solid phase. Taylor has shown
5 significant crystallization inhibition by PVP even at low levels of polymer. It was
6 reasoned that the formation of specific molecular level drug-polymer interactions [77]
7 (e.g., formation of hydrogen bonds between the PVP amide carbonyl and the
8 indomethacin (drug) carboxylic acid) contributes to physical stabilization.

9
10 Water has a low T_g (135 K, -138 °C). ASDs may be significantly plasticized if
11 they absorb substantial amounts of water. Based upon the Fox equation, it can be
12 estimated that 1% water absorbed by the polymer matrix will reduce dispersion T_g by
13 about 10 °C. Molecular mobility thereby increases, potentially facilitating crystallization
14 even at ambient temperature. Marsac et al. confirmed that the hydrophilic polymer, PVP,
15 significantly increases ASD hygroscopicity [78]. PVP hygroscopicity in some cases may
16 counteract the crystallization inhibition imparted by the high T_g polymer. It was observed
17 that nifedipine and felodipine (anti-hypertension drugs) recrystallized rapidly in PVP
18 ASDs, while displaying higher stability in ASDs with the less hygroscopic hydroxypropyl
19 methyl cellulose (HPMC) or hydroxypropyl methyl cellulose acetate succinate
20 (HPMCAS) ASDs [79]. PVP dissolves relatively rapidly in water and even more rapidly
21 at low pH, creating the potential for significant drug release in the stomach which may
22 not always be desirable.

23
24 In a unique example, PEG ASDs of the poorly soluble HIV therapeutic ritonavir
25 improved its dissolution rate at least 10-fold vs. crystalline ritonavir [80], though it has
26 been widely reported that solubility enhancement from PEG ASDs is less than that from
27 PVP ASDs [81]. This may be due to PEG's lack of strong H-bond acceptors, reducing its
28 potential for strong interactions with drugs that are H-bond donors. Zhu et al. also
29 demonstrated that crystallization onset in PEG ASDs could only be delayed and the
30 crystallization rate reduced if there were favorable interactions between the drug and
31 PEG (as for benzocaine) [82]. The most important disadvantage for PEG in ASDs is its

propensity to crystallize [83]. PEG **crystallizes** rapidly even before reaching room temperature during a melt-quenching process. Since the degree of crystallinity can increase during storage, this may result in unacceptable variation (and probable degradation) in formulation performance. Moreover, crystalline PEG has reduced ability to interact with the dispersed drug, which in turn leads to a higher propensity for drug crystallization. For example, spray-dried lactose/PEG dispersion with 10% PEG by weight had low crystallinity, but lactose recrystallized rapidly over time, transforming from amorphous lactose to the crystalline monohydrate at high humidity (75% RH) [84].

Crystallization kinetics in semi-crystalline solid dispersions are complex [85]. PEG for example may delay, promote, or have no effect on crystallization of various **active pharmaceutical ingredients** (APIs). For example, crystallization induction time of ibuprofen in a PEG matrix was actually shorter than that of pure drug, which was attributed to crystalline PEG that behaves as a heterogeneous nucleation site to accelerate ibuprofen crystallization [82]. The API in turn may greatly influence the crystallization behavior of the PEG matrix. Therefore it can be difficult to produce PEG-based solid dispersions with predictable and stable properties.

4.1.2 Hydrophobically modified polymers: poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA) and polyvinyl acetate phthalate (PVAP)

Polyvinyl polymers may be hydrophobically modified in order to reduce hygroscopicity. Free radical polymerization of vinylpyrrolidone and vinyl acetate in varying ratios leads to PVP/VA copolymers. The addition of the vinyl acetate group to the polymer backbone not only increases hydrophobicity, but also moderately plasticizes the material for easy thermal processing. PVPVA and PVP both contain carbonyl oxygens that may serve as intermolecular H-bond acceptors, but PVPVA was shown to be a more effective crystal growth inhibitor than PVP for the poorly soluble drugs celecoxib and efavirenz, mostly due to its more hydrophobic nature with lower solubility parameter values as shown in **Table 1** [86]. PVPVA may dissolve more rapidly in water than the drug component of the ASD, potentially inducing rapid drug recrystallization under non-

sink, supersaturation conditions [87].

Table 1. Solubility parameter (SP) values of polymers and model drugs investigated [86]

Polymer	SP (MPa ^{1/2})	Model drug	SP (MPa ^{1/2})
PVP	28.39	Celecoxib	23.38
PVPVA	25.77	Efavirenz	21.89

Polyvinyl acetate phthalate (PVAP) also shows potential as an ASD polymer. It is synthesized from polyvinyl acetate by partial hydrolysis, and subsequent partial esterification with phthalic anhydride. PVAP forms miscible blends with many hydrophobic APIs because it provides both H-bond donating and accepting capabilities. However, the flexible PVAP polyalkylene backbone may be less effective at interacting with solubilized drug to achieve prolonged, stable supersaturation [88].

4.1.3 Methacrylate-based copolymers: Eudragit® L, S, and E.

The Eudragit® acrylate polymer family was first developed by Rohm & Haas GmbH in Darmstadt, Germany in 1953 (now manufactured by Evonik Industries). Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acids. While Eudragit polymers displaying pH-independent behavior (e.g. the RL and RS series, containing quaternary ammonium groups) have been used in sustained release dosage forms due to their water-swelling/permeable characteristics, pH-dependent Eudragit polymers have received more attention in pharmaceutical applications.

Eudragit L and S series are important anionic polymers for use in oral drug delivery. The percentage of ionizable carboxylic acids in Eudragit L 100 (a mean of 48.3 wt% methacrylic acid, determined by potentiometric titration with NaOH solution as titrant) is higher than that in Eudragit S 100 (a mean of 29.2 wt% methacrylic acid). Carboxyl group content impacts pH-dependent solubility. L 100 starts to dissolve at pH 5.5 while S 100 becomes ionized and water-soluble at pH 7.0 [89]. To reduce burst release from an Eudragit L 100 matrix, and enhance the poor release observed from S 100

1 in the small-intestinal environment (pH 6.8), ASDs combining both polymers with poorly
2 water-soluble drugs were manufactured by melt extrusion (plasticizers usually needed) or
3 spray-drying. Mehta et al. discussed the release performance of a leukotriene D₄
4 antagonist from this amorphous blend matrix [90]. Enhanced release was achieved, and
5 more importantly, zero-order release was observed, with rate controllable by
6 **manipulating** the polymer/drug ratio.

7
8 The pH-responsive Eudragit polymers are mainly used in gastro-resistant dosage
9 forms. The exception is Eudragit E, a methacrylate/aminoester copolymer, which is
10 soluble in gastric fluid up to pH 5.0. This could be expected to provide enhanced gastric
11 delivery. Spray-dried ASDs of itraconazole with cationic Eudragit E 100 provided greater
12 increases in drug solution concentration (147-fold increase) than those prepared with
13 several pH-insensitive hydrophilic polymers (PEG 20,000, PVP and HPMC, ranging
14 from 42- to 92-fold increase) in simulated gastric media [91]. In general, due to the wide
15 variety of Eudragit polymers available, combinations of anionic, cationic, or neutral
16 methacrylate co-polymers may be employed to enhance ASD physical and chemical
17 properties.

18 19 *4.2 Cellulose and its derivatives* 20

21 Cellulose is one of the most common and widely-used polysaccharides, produced
22 in enormous quantities by plants, sea organisms such as tunicates [92], and
23 microorganisms like *Gluconacetobacter xylinus* [93]. Cellulose is a renewable
24 biopolymer of generally high molecular weight (DP ranging from 1,000 to 15,000 [94])
25 and uniform molecular composition. The structure of cellulose consists of a linear chain
26 of repeated β -D-(1 $\rightarrow$ 4) linked anhydroglucose units (AGU) (C₆H₁₀O₅)_n without any
27 branching or substituents. While cellulose is used in many industrial applications,
28 including in plastics, paper, and coatings, it is also is the basis for some of the most
29 important pharmaceutical excipients in modern drug delivery. This is in part because
30 orally administered cellulose has little or no human toxicity, and indeed is a major part of
31 human diet through consumed vegetables. Cellulose is not absorbed and at most

minimally degraded, passing through the GI tract mostly undisturbed. Direct compression of microcrystalline cellulose (MCC, DP $\approx$ 280) generates hard drug tablets with excellent compressibility [95]. As a result, MCC is frequently used as a tablet and capsule diluent in oral dosage forms.

Figure 5. Extensive inter- and intra-molecular hydrogen bonding of native cellulose

However, the uniform cellulose molecular structure with its three hydroxyls per anhydroglucose unit (AGU) results in extensive intra- and inter-molecular hydrogen bonding (H-bonding; **Fig. 5**) [96], and significant crystallinity whose magnitude depends in part upon its natural source. To disrupt crystallinity and create aqueous/organic solubility to allow convenient processing, derivatization of cellulose is required. For instance, industrial chemical preparations of cellulose esters mostly employ heterogeneous synthesis procedures by reacting cellulose suspension in organic solvent systems to a triester, followed by hydrolysis back to the desired degree of substitution (DS) (e.g. cellulose acetate propionate, Fig. 6) [97, 98]. Physical and chemical characteristics can be controlled by tuning derivative chemical structure including the type of substituent, **DS**, and average substitution patterns within the AGU. Control of these aspects offers access to a variety of materials based on cellulose with tailored properties over an expanded range, including solubility, glass transition temperature, compatibility, and optical properties.

Figure 6. Heterogeneous synthesis of cellulose acetate propionate (Note that the substituent groups are relatively randomly substituted at O-2,3,6. The specific positions of substitution shown in Figures 6, 7, and 10-15 are only for convenience of depiction and not meant to imply actual regioselectivity)

4.2.1 Conventional pH-independent cellulose esters and ethers

Cellulose derivatives are of particular interest for amorphous dispersions in part because of their high molecular weights and other physicochemical properties, as a result of which most cellulose ethers and esters cannot be absorbed from the GI tract. Even if a small degree of cellulose ester hydrolysis were to occur by chemical or lipase-catalyzed hydrolysis, the resulting by-products (cellulose, carboxylic acids, glucose) would be endogenous or dietary. Cellulose ethers are even more hydrolytically stable, and are essentially unmodified under conditions that may be experienced in the GI tract. These facts make conventional, non-ionic cellulose derivatives such as ethyl cellulose, cellulose acetate, or mixed cellulose esters (e.g. cellulose acetate propionate and cellulose acetate butyrate) even safer than synthetic polymers as hydrophobic matrices for drug delivery applications [99].

Because of their water-insolubility and lack of pH-responsiveness, simple cellulose alkanoate esters are not generally used in amorphous solid dispersions (at least not as single polymer components). It should be noted that cellulose esters such as cellulose acetate, cellulose acetate propionate and cellulose acetate butyrate are well-suited for osmotic delivery in sustained drug release systems [100]; this may not reliably result in bioavailability enhancement but is an important and demanding functional role for polymers in drug delivery. Since water insoluble polymers do not erode away over

time, in osmotic pump systems, the release of the drug is dependent on the diffusion of aqueous fluids, slowly permeating through the cellulose ester membrane. Cellulose alkanoate films tend to be quite permeable to water, and the permeability can be easily adjusted to fit particular drug properties by alternating ester degree of substitution, chain length, and the type of plasticizer. Changes in pH or salt content of the surrounding physiological environment do not influence the delivery rate due to the impermeability of the polymer membrane to salts. Cellulose diacetate (DS(Ac) ca. 2.5) is very frequently used to form the semi-permeable membrane, for example in sustained release of acetaminophen [101], theophylline, dyphylline, and proxiphylline [102]. Increasing the percentage of cellulose acetate in the dosage form (CA-to-drug weight ratio) can further prolong the release of the drugs due to reduction in water permeation rate. Release in so-called elementary osmotic pump systems is controlled largely by the diameter of a laser-drilled hole through the CA coating, but in later versions rate can be controlled in the absence of laser drilling by controlling film porosity during the formulation [103]. In one example of how to do this, the solid formulations were pressurized under carbon dioxide gas to form pores in place of the bubbles upon release of pressure. Microspheres with large internal cavities showed higher release rates.

Beyond osmotic delivery, blends of pH-independent cellulosic polymers with pH-dependent ones (e.g. CAPhth, HPMCP) (properties in **Table 2**) are being developed for desirable drug release properties [104].

Table 2. Properties of cellulose esters used in pharmaceutical formulation, reproduced with permission from Ref. [100]; Copyright 2006 Springer.

CE	Abbrev.	DS ^a (Ac)	R ^b	DS (R)	T _g (°C)	Solvents	M _n (/1000) ^c
Cellulose acetate	CA- 398-NF	2.5	NA	NA	185	Acetone	40
Cellulose acetate butyrate	CAB- 171-15	2.0	Butyryl	0.8	161	Acetone, ethyl acetate	65

Cellulose acetate phthalate	CAPhth	2.1	Phthaloyl	0.9	175	Acetone/water, ethanol/water	13
Hydroxypropyl methyl cellulose phthalate	HPMCP 55	NA	Hydroxypropyl Methyl Phthaloyl	0.3 1.9 1.7	135	Acetone/water, ethanol/water	20

1 a. DS: Degree of substitution per anhydroglucose unit.

2 b. R: substitution groups.

3 c. M_n : number-average molecular weight.

4

5 **Hydroxypropylmethylcellulose (HPMC)**

6 Cellulose ethers, including carboxymethylcellulose, methyl and ethyl cellulose,
7 and hydroxyethyl and hydroxypropyl cellulose and derivatives perform a variety of
8 functions such as thickening, binding, and water retention in pharmaceutical and personal
9 care products. Commercial cellulose ethers are usually water-soluble (ethyl cellulose is
10 an exception), and so can modify aqueous solution rheology. The water-soluble cellulose
11 ether HPMC is not pH-responsive, unlike most other cellulose derivatives useful for
12 ASDs. It also lacks very strong H-bond donor or acceptor groups [105].

13

14 HPMC, also referred to as hypromellose, is generally prepared by processing
15 cellulose, dissolving pulp in sodium hydroxide solution, followed by reaction with
16 methyl chloride and racemic propylene oxide at the same time in a heterogeneous process,
17 affording cellulose etherified with methyl, hydroxypropyl, and oligo(hydroxypropyl)
18 substituents [106]. Because of the potential variation in oligo(hydroxypropyl) chain
19 length, and because of the potential for alkoxide addition at either the methylene or
20 methine end of the propylene oxide epoxide (least hindered end is most favored, but not
21 exclusively), the structure of the HPMC co-polymer is extremely complex, so much so
22 that it cannot be completely ascertained by current analytical methods. As a result HPMC
23 is an amorphous polymer with a T_g that is very broad and difficult to measure.

24

25 In spite of its inability to engage in strong specific interactions with drug molecules due
26 to the absence of carboxylic acid or amide functionality, HPMC has proven useful for

ASD formulation with various drugs. Bioavailability studies with ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor, showed a surprising 100-fold increase in both $C_{\max}$ and AUC of an HPMC ASD formulation compared with the pure drug, using male beagle dogs [107]. HPMC stabilized the amorphous drug in the solid state, even though the presence of the hygroscopic HPMC in the solid dispersion caused it to absorb 2 wt% moisture when equilibrated at 75% RH, which might have been expected to induce recrystallization. Suzuki et al. evaluated nifedipine (a calcium-channel agent) solid dispersions with four water-soluble polymers; HPMC, PVP, partially hydrolyzed polyvinyl alcohol (PVA), and pullulan [108]. HPMC prevented nifedipine from crystallizing from the solid dispersion, and provided the highest supersaturation level among these polymers in dissolution studies. Solubility parameter (SP) was introduced here as a criterion for selection of the polymeric matrix; in this case the SP value of HPMC was the closest to that of nifedipine.

A commercial product, Intelence[®] (etravirine, an anti-HIV drug) was commercialized by Janssen Pharmaceuticals in 2008 as a spray dried ASD with HPMC. Etravirine is an extremely poor glass former and its amorphous state is very unstable, consistent with its high T_m of 265 °C. As evidenced by powder X-ray diffraction (XRD), solid-state NMR, as well as visualization techniques including scanning electron microscopy and atomic force microscopy, spray-drying with HPMC was the only formulation method (compared to other amorphous dosage forms) that afforded stabilization of amorphous etravirine, and enhanced bioavailability [109]. The higher the percentage of HPMC present in the etravirine ASD, the better solid-phase stability was observed. Recently the Taylor group further studied the ability of HPMC to inhibit recrystallization of felodipine from supersaturated solutions [110]. The presence of a small amount of pre-dissolved HPMC (as low as 0.5 µg/mL) could inhibit both nucleation and growth of felodipine crystals, with effectiveness depending on the extent of supersaturation.

4.2.2 pH-Responsive cellulose derivatives

1 In order to take full advantage of the aforementioned low toxicity, generally high
2 T_g values that help prevent drug migration and crystallization, and rigidity of cellulose
3 and its derivatives [111] for ASD matrices, it is desirable to modify the polymer to create
4 a trigger for drug release, and structural features that may enhance affinity for drugs
5 through specific interactions. One type of trigger may be swelling or dissolution upon
6 contacting the aqueous media of the GI tract. There are two common ways of achieving
7 water swellability for cellulose derivatives: prepare a derivative with high DS(OH), or
8 append polar and/or ionizable groups. Cellulose is inherently very hydrophilic, and a low
9 DS of nearly any substituent, even non-polar ones, can disrupt H-bonding and thereby
10 impart water solubility. A typical design object is an amphiphilic cellulose derivative
11 which contains pendent carboxylic acids to provide a pH trigger mechanism for swelling
12 and drug release under the near-neutral pH conditions of the intestines [100]. These polar
13 groups also provide energetically favorable specific interactions by H-bonding with
14 moieties on drug molecules, for example amine groups that are components of many
15 drugs [112].

16
17 Carboxy-containing cellulose derivatives are fully protonated and therefore
18 insoluble in the low pH (1-3) of the stomach, but are ionized in the higher pH (5.5-7) of
19 the small intestine (e.g. succinate groups of HPMCAS have pK_a of ~ 5 [113],
20 carboxymethyl groups of CMC have pK_a of ~ 3.7 [114]). This can enable a drug-polymer
21 ASD to remain intact when passing through the stomach to limit contact between drug
22 and gastric acid or digestive enzymes, but swell and dissociate to enable the active
23 contents to release, dissolve and be absorbed in the small intestine. Carboxylic acid
24 substituents can provide additional benefits in ASDs, as described for the specific
25 polymers below.

26
27 **Carboxymethyl cellulose derivatives: Carboxymethyl cellulose acetate butyrate**
28 **(CMCAB)**

29
30 Carboxymethylcellulose (CMC) is the most important anionic, water-soluble
31 cellulose ether, produced in large quantities by etherification of activated alkali cellulose

with chloroacetic acid [115]. Conversion of carboxymethylcellulose into hydrophobic ester derivatives like acetate, propionate and butyrate has been reported by inventors from Eastman Chemical Company (**Fig. 7**) [116].

Figure 7. Two-step preparation of CMCAB with DS (CM) 0.33

Allen and co-workers prepared these CMC mixed esters with various DS (alkanoates), depending on the feed ratios and reaction conditions [116, 117]. The commercially produced CMCAB polymers had DS (CMC) of 0.29 to 0.35, DS (butyryl) of 1.37 to 1.64 and DS (Ac) of 0.30 to 0.55 [99]. **Fig. 7** shows the chemical structure and DS (alkanoate) values for Eastman CMCAB-641-0.2. The high DS of acyl groups provides good solvent solubility, and at the same time provides relatively broad miscibility with hydrophobic drugs. While the pendent CMC groups do provide pH sensitivity and swelling at neutral pH, the rather low DS (CMC) (ca. 0.3) is insufficient to provide bulk solubility in water.

Posey-Dowty et al. described two distinct potential methods of employing CMCAB for oral drug delivery [11, 118]. They found that it was possible to make physical blends of CMCAB with drugs by simple direct compression using a single tablet press. Physical blends of ibuprofen with CMCAB gave extended, zero-order drug release at pH 6.8 (**Fig. 8**). Release that is zero-order with respect to time can afford relatively constant blood levels of a medication, which is often therapeutically desirable. These zero-order CMCAB formulations could be a simple and inexpensive way to create once-

a-day formulations for enhanced patient convenience and adherence to dosage regimen. In the case of ibuprofen this was contrasted with complete dissolution of ibuprofen from a physical blend with microcrystalline cellulose within 30 min at pH 6.8.

Figure 8. Ibuprofen release with physical blends of CMCAB vs. microcrystalline cellulose (MC), reprinted from Ref. [11]; Copyright 2006 Springer.

Figure 9. Comparison of fexofenadine HCl release from physical blend of CMCAB/drug vs. capsule containing amorphous formulation, reprinted with permission from Ref. [118]; Copyright 2010 American Chemical Society.

For miscible, poorly water-soluble drugs, for example fexofenadine HCl (antihistamine), intimate mixing afforded largely or entirely amorphous drug dispersed in a CMCAB matrix. The drug and CMCAB were co-dissolved in an organic solvent, then ASDs were prepared by a number of techniques including co-precipitation and solvent

evaporation (rotary evaporation, spray drying or film casting) [118]. XRD was used to confirm the amorphous nature of the drug in CMCAB dispersion. CMCAB is thermodynamically miscible with many pharmaceutical actives, as predicted by Hansen 3D solubility parameters. Differential scanning calorimetry measurements detected only a single glass transition temperature, further indicating good compatibility. It was identified that drug release from these molecular blends was slow, as expected, at simulated gastric pH, but release was complete and nearly zero-order at simulated intestinal pH (6.8, **Fig. 9**). Drug solution concentrations were substantially enhanced from CMCAB ASDs at neutral pH, while the physical blends gave poor dissolution performance.

In addition to drug delivery, CMC esters are valuable materials for waterborne coatings applications [119]. However, published synthetic methods for synthesis of CMCAB create concern about possible polymer crosslinking. Strong acid catalysts (e.g. sulfuric acid) are necessary for appending alkanoate esters to CMC by reaction with carboxylic acid anhydrides. Under such conditions, the CMC carboxyl group could be expected to react directly with free hydroxyls, or as a mixed anhydride with the alkanoate, to form a crosslinked gel. CMC is also vulnerable to crosslinking by multivalent ions (**Fig. 10**) [120], and the same could be expected for CMCAB.

Figure 10. Potential CMCAB crosslinking mechanisms; (1) acid-catalyzed (2) multivalent cations

Cellulose phthalate derivatives: cellulose acetate phthalate (CAPHth) and hydroxypropylmethylcellulose phthalate (HPMCP)

Cellulose acetate phthalate (CAPHth) was firstly identified as a pH sensitive coating polymer by Malm et al. at Eastman Kodak Company more than 70 years ago [121]. A pH sensitive coating is defined as a material that is insoluble at low pH and swells and/or dissolves at neutral to high pH. CAPHth is well-suited to this application because it is soluble in organic solvents and acts as a good film-former; furthermore, it has the ability to form water-soluble salts readily with ammonia, creating the potential for solvent-free coating. Malm prepared CAPHth esters by reaction of cellulose acetate ($DS_{\text{acetyl}} = 1.77$) in glacial acetic acid with phthalic anhydride [122] catalyzed by mild bases (sodium acetate or pyridine) for 6 hours at 95 °C; phthalate DS ranged between 0.42 to 0.96. Due to its ionization at relatively low pH, CAPHth has been explored as a matrix for amorphous dispersions [88]. *In vivo* testing conducted in Sprague-Dawley rats demonstrated a significant 2-fold improvement in oral bioavailability from a CAPHth/itraconazole ASD (2:1 polymer:anti-fungal drug ratio) compared to Sporanox®, the marketed dosage form of itraconazole. The CAPHth-based formulation also outperformed ASDs using the chemically related PVAP. The authors reasoned that the more rigid cellulosic polymer backbone could sterically hinder drug recrystallization, affording improved stabilization [88].

HPMCP dissolves in water at either pH 5 or pH 5.5, depending on the grade. Kai et al. studied oral bioavailability of MFB-1041 (a triazole antifungal agent) upon ASD formulation with HPMCP (5:1 polymer-to-drug ratio) [123]. Maximum drug solution concentration (pH 6.8) was increased by a factor of 12.5 as compared to that from micronized drug powder, and oral bioavailability was enhanced nearly 17-fold. HPMCP enhanced the dissolution rate, but was ineffective at inhibiting recrystallization. Maximum concentration was achieved within 5 min followed by rapid desupersaturation, resulting in only 3-fold increase in apparent solubility vs. that of a microcrystalline

dosage form after 4 hours. This might be in part due to the difference in solubility parameters between the polymer and MFB-1041 (weaker interactions).

There are only a few reports on ASD application of these cellulose phthalate polymers, likely because CAPHth and HPMCP have relatively limited miscibility with organic drug molecules. As a consequence, researchers have explored other cellulose derivatives in search of more broadly useful ASD polymers.

Cellulose succinates: hydroxypropyl methylcellulose acetate succinate (HPMCAS)

Amphiphilic, water-dispersible cellulose succinate mixed esters were first reported by Eastman Chemical Company [124]. Cellulose acetate butyrate (CAB-553-0.4) is prepared by acid-catalyzed bulk reaction with butyric anhydride in acetic acid. The CAB is reacted in a separate step with succinic anhydride under mild alkaline conditions to afford cellulose acetate butyrate succinate (CABSu, Eastman commercial designation “CAB-SU160”) (**Fig. 11**). The purpose of acylation with succinic anhydride in a separate, weak-base catalyzed step is to avoid acid-catalyzed crosslinking between a hydroxyl group on one chain and a carboxylic acid on another chain. The succinoyl groups ($DS_{Su} = 0.38$) enhanced the water affinity of these cellulose esters, particularly when neutralized by amines, while the acetate and butyrate groups ($DS_{Ac} = 1.9$, $DS_{Bu} = 0.1$) provided hydrophobicity, affinity for hydrophobic small molecules, and water insolubility at low pH [99]. This cellulosic material was only studied as a rheology modifier for waterborne coatings; there are no reports of using CABSu as ASD polymeric matrix. The hydrolytic instability of CABSu may be a concern for such applications.

Figure 11. Industrial preparation of CABSu from CAB-553-0.4

HPMCAS is prepared by reacting HPMC with acetic and succinic anhydrides [125]. HPMCAS has a rather complex structure, with four substituent types that are likely to be relatively randomly distributed around the anhydroglucose unit and along the cellulose chain (**Fig. 12; Table 3**) [126]. The hydroxypropyl substituent carries the additional complication that it can generate oligomeric poly(hydroxypropyl) side chains of various lengths and connectivity, as mentioned in the HPMC discussion. This leads to potential complexities with regard to manufacturing control and product analysis. Unlike cellulose succinate, HPMCAS is essentially insoluble in water at pH < 5 (which may be important to stabilization of supersaturated drug solutions against crystallization) due to the presence of relatively hydrophobic methyl and acetate groups, and remains colloidally stable against hydrophobic aggregation when the succinate group is largely ionized at intestinal pH (ca. 5.5-7.5) [113]. The amphiphilic nature of HPMCAS enables strong interaction with hydrophobic drugs, and enables it to form stable dispersions in aqueous media.

Figure 12. Chemical structure of HPMCAS

Table 3. Composition of HPMCAS from Shin-Etsu Chemical Co., Ltd. [127]

Substituent	Degree of substitution
Methoxy (Me) + Hydroxypropyl (HP)	2.17*
Acetate (Ac)	0.31-0.51
Succinate (Su)	0.12-0.33

*Molar substitution used for hydroxypropyl due to chain extension ability

1
2 HPMCAS has been extensively studied and is now used, including in marketed
3 formulations, as an ASD matrix polymer for drug solution concentration enhancement.
4 Much of the early work was carried out by workers from Pfizer Inc. and Bend Research
5 [128]. They report solution concentration enhancement of basic or zwitterionic drugs,
6 such as ziprasidone hydrochloride, by simple admixing with HPMCAS in solution of at
7 least 1.5-fold. Other studies showed a 28-fold increase in dissolution rate from an ASD of
8 HPMCAS with AMG 517 (a highly selective TRPV1 antagonist) compared to crystalline
9 drug only, and a nearly 2-fold increase compared to amorphous drug [129].

10
11 HPMCAS was identified as a highly effective drug carrier in a solid dispersion
12 with nifedipine [130]. First, to achieve an ASD, the required amount of HPMCAS was
13 less than that required for PVP or methacrylic acid ethyl acrylate copolymer. The
14 hydrophilic substituents of HPMCAS lead to a moderate amount of moisture absorption
15 depending on the particular DS/MS values of the individual grade, but generally
16 HPMCAS absorbs much less water than PVP and PEG [79]. Despite the potential impact
17 of HPMCAS hygroscopicity upon nifedipine/HPMCAS ASDs, nifedipine nucleation rate
18 was still observed to be much lower from these ASDs than that of the amorphous drug
19 without polymer [111]. The HPMCAS combination of hydrophobic, hydrophilic, and
20 ionizable carboxyl groups frequently affords sufficiently strong polymer-drug interactions
21 to stabilize drugs against crystallization from solution or from the solid dispersion prior
22 to drug release. In the cited examples, HPMCAS-based solid dispersions also
23 demonstrated better drug solution concentration enhancement than the other ASD
24 polymers examined. Drug release behavior could also be manipulated by altering the
25 ratio of hydrophilic succinoyl and hydrophobic acetyl moieties [130, 131].

26
27 It is also notable that nifedipine in spray-dried HPMCAS-based dispersions was
28 stable against precipitation after dissolution. When the dispersion was introduced to
29 medium simulating the lumen of the duodenum and small intestine, amorphous
30 drug/polymer nanostructures, termed as nanoaggregates, were formed. Those stable
31 nanoaggregates were described as the key reason for enhanced and sustained free-drug

concentration and absorption in the intestinal lumen [113]. Hillmyer et al. further synthesized esters of HPMC with hydrophobically substituted succinates (**Fig. 13**) and formulated spray-dried ASDs with phenytoin (antiepileptic, equilibrium solubility 27.1 $\mu\text{g/mL}$) [132]. In order to achieve a high level of supersaturation (high maximum solution concentration) and maintain it against precipitation (high bioavailability) through the effective GI absorption zone, Hillmyer found that the optimal cellulose derivatives among those studied contained a sufficiently high DS of substituted succinate and a combination of thioether and weakly electron-withdrawing groups (e.g. cyclohexyl, benzyl) as the hydrophobes.

Figure 13. Derivatization of HPMC with hydrophobically substituted succinates as polymer matrix for oral drug delivery, reprinted with permission from Ref. [132]; Copyright 2014 American Chemical Society.

It must be noted that the manufacturing of HPMCAS may be difficult to control due to the potential for variable chain extension of the hydroxypropyl group. Ring opening of propylene oxide by an alkali cellulose salt affords a pendent hydroxypropyl group as its alkali metal salt. This alkoxide is separated from the cellulose main chain and so is a stronger nucleophile than are the salts of the main chain OH groups, due to wider available approach angles. Therefore the next molecule of propylene oxide is more likely to react with the pendent group, thereby growing an oligo(propylene oxide) chain of variable length. The terminal OH groups of these chains in the isolated product may also react preferentially with acetic or succinic anhydride in the subsequent step. These multiple sources of variation (e.g. multiple substituents, positions of substitution, oligomer lengths) create significant challenges for consistent HPMCAS manufacture and

1 for complete and accurate analysis.

2
3 Recently, the tetrablock polymers poly(MA-stat-CEA-stat-HPA-stat-PAA) were prepared
4 using RAFT polymerization based on the concept of “controlled statistics” by Reineke et
5 al. [133]. By including monomers, each of which contained a substituent that is also
6 appended to HPMCAS (methoxy, hydroxypropyl, acetyl, succinoyl, and glucose units),
7 the multicomponent copolymers based on acrylics with uniform molecular weights and
8 well-defined chemical compositions might provide insight into HPMCAS
9 structure–property relationships, but in a more readily controlled system. Reineke and co-
10 workers found that the molecular interactions provided by increased amounts of ionizable
11 carboxylic acid and hydroxyl groups contributed to solid and solution phase stabilization
12 of probucol (anti-hyperlipidemic drug, log P 8.9) [134].

13
14 The hydrolytic stability of the succinoyl esters in cellulose succinate derivatives
15 in aqueous solutions is always a potential concern, especially for dispersion applications
16 (e.g. coatings) in which amines are frequently used. Kinetic studies have been performed
17 by Edgar et al. using aqueous solutions of cellulose acetate butyrate succinate (CAB-
18 SU160) in the presence of dimethylaminoethanol [135]. They demonstrated that the
19 succinoyl groups were hydrolytically removed at a surprisingly rapid rate under neutral or
20 slightly alkaline conditions (**Fig. 14**), with rates increasing with amine concentration. It
21 was reasoned that auto-catalyzed hydrolysis of the succinoyl group would be promoted
22 by an energetically favorable 5-membered ring transition state [136]. This issue should
23 not be neglected when designing carboxyl-containing polysaccharides for ASD usage,
24 especially since commercial viability of such polymers is often dependent on developing
25 other uses where hydrolytic stability demands are greater.

Figure 14. Proposed CAB-Su hydrolysis mechanism [135]

Cellulose ω -carboxyesters: cellulose adipate/suberate/sebacate derivatives

Edgar et al. developed a family of novel cellulose ω -carboxyesters, which were purpose-designed for use in ASDs, unlike all other polymers used commercially in ASDs and most polymers under investigation for ASD usage [136-138]. The potential for carboxyester auto-catalyzed hydrolysis should be minimized, since such a process would require an unfavorable 7-membered or larger ring transition state for the longer chain ω -carboxyesters studied. Two synthetic methodologies were explored. Direct synthesis of cellulose adipate derivatives by reaction with adipic anhydride is a one-step reaction beginning with commercial materials; however, it is complicated by *in situ* formation of poly(adipic anhydride) due to homopolymerization of adipic anhydride. Subsequent reaction of the poly(anhydride) with hydroxyls on different cellulosic chains resulted in substantial crosslinking and gelation, leading to insoluble polymers that were not useful for ASD application. This crosslinking proved to be preventable by careful purification of the adipic anhydride and specific modifications of the synthetic procedure. A second route was also designed to circumvent these potential difficulties, involving reaction of cellulose or cellulose esters with C6-C10 diacids that have been monoprotected as benzyl esters at one end, and monoactivated as acid chlorides at the other. Palladium-catalyzed hydrogenolysis of the resulting cellulose benzyl ω -carboxyalkanoates afforded the

deprotected carboxy-terminal alkanoates under mild conditions; the products showed no spectroscopic evidence of crosslinking and were highly solvent-soluble (**Fig. 15**). In this way high T_g cellulose adipate, suberate and sebacate esters were synthesized, providing a versatile cellulose ω -carboxyalkanoate family (including longer chain lengths like sebacate that are unavailable by reaction with cyclic anhydrides) for ASD formulations.

Figure 15. Synthesis of cellulose ω -carboxiesters, reproduced from Refs. [137, 138];
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The relative ability of these structurally diverse cellulose ω -carboxiesters to stabilize lipophilic drugs (celecoxib, efavirenz, and ritonavir) in solution against nucleation [139] and crystal growth [86, 140] was studied by Taylor et al. To disrupt the reorganization of a cluster of solute molecules into an ordered crystal structure and further prevent crystal growth on the surface of formed drug crystal, polymer-solute interactive forces were determined to be a major factor. The polymers with effective inhibitory effects were found to have an optimal level of hydrophobicity relative to that of drug molecules and specific intermolecular interactions, mostly provided by a high number of ionized carboxylate groups (COO^-) at pH values reflecting the intestinal environment. High DS(carboxyester) was also found to be important for crystallization inhibition by other researchers [132, 141].

5. Concluding remarks and outlook

Use of polymers (and oligomers) to enable solubility enhancement of hydrophobic pharmaceutical actives has been an area of strong interest for polymer scientists. Methods including cyclodextrin complexation, nanoparticles stabilized by

1 polymers, lipid formulation with polymeric surfactants, and polymer micellar
2 solubilization have proven to be effective approaches. Among these approaches,
3 amorphous solid dispersion formulation shows the potential to be a uniquely potent and
4 broadly applicable technology. Drugs are intimately blended with suitable polymeric
5 additives to form amorphous solids, which typically lead to supersaturated solutions upon
6 release. The increase in solution concentration creates enhanced chemical potential of the
7 drug across the GI epithelium, leading to enhanced permeation into the bloodstream and
8 hence bioavailability enhancement. Unlike many traditional strategies to increase the
9 equilibrium solubility of highly lipophilic drugs including cyclodextrin complexation,
10 micellar solubilization and cosolvent addition, both drug solution concentration and
11 permeation are enhanced by the ASD method.

12
13 The utility of cellulose derivatives in oral drug delivery applications, especially
14 for amorphous solid dispersions discussed above, has been well-established in the
15 literature. Drug solubilization, drug stabilization and enhanced drug release provided by
16 the polymeric additives including those cellulose derivatives are of great importance.
17 However, enhancing solubility and bioavailability of lipophilic active pharmaceutical
18 ingredients as amorphous solid dispersions is still a difficult frontier. Any single drug
19 candidate has its own unique physical and chemical properties, therefore there can be no
20 universal formulation. With increasing abundance and diversity of drug candidates,
21 development of novel polymer excipients for solubility enhancement formulations is
22 highly important. As described above, synthetic polymers (PVP, PEG) and existing
23 cellulose derivatives (CMCAB, HPMC and HPMCAS) are not purpose-designed for
24 ASD and thus do have a number of limitations as described. Designing and producing
25 novel carboxyl-containing cellulosic materials with enhanced properties (e.g. easier
26 manufacturing process, better chemical stability, higher level of molecular interactions
27 with drugs) will allow pharmaceutical scientists to maximize the advantages of
28 amorphous solid dispersions. Moreover, it is anticipated that developing a broad family
29 of advanced cellulose derivatives with easy-to-tune structures will further result in better
30 control over the performance of oral drug formulations.

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