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Feature article

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.

Contents

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1. Scope

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

2. Oral drug delivery and impediments thereto

The majority of drugs are administered by the oral route; as tablets, capsules, or solutions. Why is oral administration so often the method of choice for providers and patients? Oral drug delivery is typically preferred vs., e.g., intravenous injection, in part because it allows *administration* of precise doses, is inexpensive since administration usually can be done by the patient, and is generally comfortable for patients, leading to relatively high patient adherence to dosage regimes. Due to its large surface area, the small intestine is the primary absorptive organ for drugs in the human body. Although stomach-specific drug delivery is desired in some cases (for example, floating beads containing clarithromycin were designed to be delivered to the stomach site against *Helicobacter pylori*) [1], many drugs are degraded in gastric media where the pH may be 2 or less, depending on patient age, health, diet, fed/fasted state, and potentially on other drugs being taken by the patient. Meanwhile some drugs, such as aspirin and ibuprofen, 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 → 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 pharmaceutical formulations to improve solubility of lipophilic drugs [13]. Complex formation often involves addition of the drug to an aqueous CD solution, spontaneously forming the soluble CD complex. Then the solid complex can be isolated from the solution by methods such as co-precipitation or spray-drying. Solid complexes so obtained can be easily reconstituted as solutions by adding water or saline for intravenous administration. The major product of enzymatic synthesis from starch is β-CD (cyclic heptamer), which is therefore most efficiently produced and has generally broad binding affinity for hydrophobic drug solutes [14]. For these reasons β-CDs are the most widely used for preparation of CD-drug complexes. However, β-CD is favorably oriented to form intramolecular hydrogen bonds, resulting in a

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