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Review

Mechanisms by which cyclodextrins modify drug release from polymeric drug delivery systems

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Abstract

For many drug candidates a modified in vivo drug release is desired to improve efficacy, sustain effect or minimise toxicity. Polymeric delivery systems, such as microspheres, nanospheres and polymeric films, have been extensively researched in an attempt to achieve modified drug release. Cyclodextrins offer an alternative approach. These cyclic oligosaccharides have the ability to form non-covalent complexes with a number of drugs and in so doing alter their physicochemical properties. In addition, the primary and secondary hydroxyl groups of the native (α, β, γ-) cyclodextrins are potential sites for chemical modification. It follows that the incorporation of these agents into polymeric drug delivery systems, as physical mixtures, covalently bound conjugates or cross-linking agents, frequently permits a greater degree of control of drug release. This paper reviews the incorporation of various cyclodextrins into polymeric formulations. The mechanisms by which cyclodextrin/polymer formulations act to modify drug release are considered.

Keywords: Cyclodextrin; Microspheres; Polymer; Modified release; Mechanism

1. Introduction

1.1. Polymeric drug carriers

The therapeutic benefit of a number of drugs administered in traditional dosage forms is sometimes limited by physiological barriers, undesirable physicochemical drug properties or issues of drug toxicity. In such cases the development of drug delivery systems that produce a modified in vivo drug release is a common research aim. By manipulating the release of drug from its dosage form such restrictions may be overcome and an improvement in therapeutic effect observed.

The ability of polymers to modify drug release is well known. Several polymer-based controlled delivery devices, such as MST Continus® (morphine sulphate) and Brufen Retard® (ibuprofen),

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have achieved both improved clinical outcomes and considerable market success. Polymers also form the basis of many gels, microspheres and nanospheres. These formulations have gained increasing prominence in recent years (Allémann et al., 1993; Couvreur et al., 1995; Merkli et al., 1995; Okada and Toguchi, 1995; Kellaway and Warren, 1996).

The mechanisms of drug release from polymeric systems are discussed at length by Baker (1987), Chasin and Langer (1990), Benita (1996) and Washington (1996). The three most common mechanisms by which release of drug from these systems occur are: dissolution, diffusion and, erosion. Importantly, the description of a delivery device as dissolution, diffusion or erosion-controlled may only refer to the dominant though not exclusive mechanism of release. Attempts to model release data from such systems are widespread and have been described by Rosoff (1988), Washington (1990), Vergnaud (1993), Ju et al. (1995) and Papadokostaki et al. (1998a,b).

Problems controlling drug release from polymeric carriers are common, particularly for matrices composed of hydrophilic polymers that have a high surface area to volume ratio. In such cases, drug release from the carrier may be rapid and characterised by a 'burst' release (Pongpaibul et al., 1988; Leucuta et al., 1997). Narasimhan and Langer (1997) quantitatively described this 'burst effect' during essentially zero-order drug release from coated hemispherical polymeric carriers. This analysis showed burst release was controlled by the solubility of drug in the release medium, the drug diffusion coefficient and the initial drug distributions within the polymeric carrier. Rapid swelling or dissolution of the polymer matrix will also promote a burst release.

The incorporation of cyclodextrins into polymeric matrices may overcome such limitations.

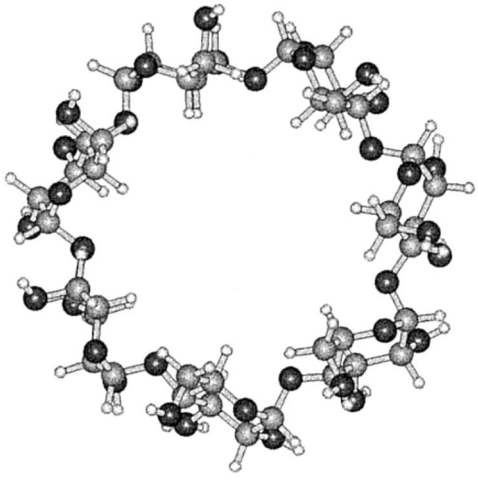

Fig. 1. Structure of β-cyclodextrin (β-CD). Carbon atoms: light shading; oxygen: dark.

1.2. Cyclodextrins

1.2.1. Parent cyclodextrins

Cyclodextrins are a group of cyclic oligosaccharides obtained from the enzymatic degradation of starch. The three major cyclodextrins α-, β- and γ- (CD) are composed of six, seven or eight D-(+)-glucopyranose units, respectively. These agents have a torus structure, with primary and secondary hydroxyl groups orientated outward (Fig. 1). Consequently, cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. This cavity enables cyclodextrins to complex 'guest' drug molecules and in so doing alter the physicochemical properties of the drug. The aqueous solubility of a drug-cyclodextrin complex in particular, can be dramatically different to that of the free drug. For example, the water solubility of tretinoin is small (8×10^{-3} mg/100 ml), but can be increased up to 2.7×10^{3} mg/100 ml through complexation with β-CD (Montassier et al., 1997). This ability of cyclodextrins to form inclusion complexes can occur both in solution and in the solid state (Szejtli, 1988), provided the guest substrate is sterically compatible and fulfils charge and polarity criteria.

The forces driving complexation have been attributed, amongst other things, to: the exclusion of high energy water from the cyclodextrin cavity; the release of ring strain, particularly in the case of α-CD; van der Waals interactions; hydrogen and hydrophobic binding (van Helden, 1992; Ross

and Rekharsky, 1996). The complexation of drug with cyclodextrin can be defined by an association constant (K_{assoc}), given the following formula:

$$[\text{Drug}] + [\text{CD}] \overset{K_{assoc}}{\rightleftharpoons} \frac{[\text{Drug-CD}]}{[\text{Drug}][\text{CD}]} \quad (1)$$

where [Drug] and [CD] represent the free concentration of drug and cyclodextrin and [Drug-CD] is the concentration of the complex. No covalent bonds exist between the cyclodextrin and its guest, so complexation can be considered a dynamic process. A drug included within the cyclodextrin cavity may therefore be dissociated upon dilution, displaced by a more suitable guest or transferred to a matrix for which it has a higher affinity, such as a biological membrane (Loftsson and Brewster, 1997). The association constants for a range of compounds with cyclodextrins are listed in the supplementary material of Connors (1995).

1.2.2. Cyclodextrin derivatives

The most widely used of the native cyclodextrins, β-CD, is limited in its pharmaceutical application by its low aqueous solubility (1.85 g/100 ml at 25°C; Szejtli, 1988) and toxicity profile. However, the hydroxyl groups on the exterior ring of native cyclodextrins are available for chemical reaction. Derivatives such as hydroxypropyl-β-CD (HP-β-CD; Encapsin®) and sulphobutylether-β-CD (SE-β-CD; Captisol®) which is anionic, have therefore been synthesised to produce more water-soluble and less toxic entities (Irie and Uekama, 1997; Stella and Rajewski, 1997).

Cyclodextrin derivatives have a number of applications. Both HP-β-CD and SE-β-CD for instance, have been shown to substantially improve the oral bioavailability of cinnarizine in dogs (Järvinen et al., 1995). Drug-cyclodextrin conjugates have also been formulated as prodrugs to promote a delayed-release of the NSAID biphenylyl acetic acid in rats (Hirayama et al., 1996; Minami et al., 1998).

A retarded drug release, through dissolution-limited mechanisms, is a common objective for the use of many poorly water-soluble cyclodextrin complexes. Lemesle-Lamache et al. (1996a,b) for example, demonstrated a slower in vitro dissolution of salbutamol in water, when prepared as tabletted complexes with five types of ethylated β-CD of different degrees of substitution and aqueous solubility. This was attributed to a decrease in solubility for the derivatised cyclodextrin complexes compared to the free drug. A correlation was noted between the profiles of sustained release for the various ethylated β-CDs and the observed values of K_{assoc}, but not with the degree of substitution or the aqueous solubility of the ethylated cyclodextrins. It was proposed that a slow dissolution of drug (i.e. sustained release) could be achieved from a poorly water-soluble complex if K_{assoc} was sufficiently high.

Horikawa et al. (1995) took the concept of dissolution-limited release a step further through the preparation of a delayed-release compressed tablet composed of molsidomine complexed with *O*-carboxymethyl-*O*-ethyl-*O*-β-CD (CME-β-CD). The in vitro release rate of the vasodilator was suppressed at low pH, but increased with increasing pH. This was attributed to the higher solubility and dissolution rate of CME-β-CD at higher pH values, due to ionisation of its carboxyl group ($pK_a \approx 4$). Plasma levels following administration of the tablet to beagle dogs showed retarded absorption in those animals with a high-gastric acidity compared to a low-gastric acidity, though AUC's were similar. Clearly, CME-β-CD showed potential as a delayed-release carrier, where the release rate of the water-soluble drug is reduced in the stomach and increased at its main site of absorption, the small intestine.

Information on the use of cyclodextrins to modify drug solubility or improve drug stability, bioavailability or toxicity profiles can be found in a number of books and reviews (Szejtli, 1988, 1990; Albers and Müller, 1995; Loftsson and Brewster, 1996; Rajewski and Stella, 1996; Thompson, 1997).

2. Cyclodextrin and polymers: considerations

The incorporation of cyclodextrins into polymeric drug delivery systems can influence the mechanisms by which drug is released. Physically mixed and complexed cyclodextrins for example,

can modify drug solubility or diffusivity, improve hydration of the polymer matrix or promote its erosion. However, when incorporated into polymeric delivery systems the potential of cyclodextrins to form stable drug-cyclodextrin complexes may be restricted. Significantly, the presence of organic solvent residues may weaken the drug-cyclodextrin complex. Mulski and Connors (1995) for instance, demonstrated decreases in the K_{assoc} of a 4-nitroaniline-α-CD system of > 30-fold when prepared in a variety of aqueous-organic binary solvents. Solvents such as acetone and various alcohols are frequently used in the production of polymer matrices and their complete removal from the product can be difficult. In addition, cyclodextrins are known to complex with the polymers themselves. Poly(ethylene glycol) and poly(ethylene oxide) derivatives have been shown to complex with cyclodextrins (Amiel and Sebille, 1996; Harada et al., 1997) and a supramolecular structure, in which γ-CD is threaded along a poly(tetrahydofuran) polymer backbone, was proposed by Harada (1997). The physical presence of polymers capable of inclusion within the cyclodextrin cavity would be expected to hinder the ability of cyclodextrins to complex otherwise suitable drugs. However, a reduction in the drug-cyclodextrin K_{assoc} is not always observed. Siguroardóttir and Loftsson (1995) demonstrated an increase in the K_{assoc} of the complex formed between hydrocortisone and HP-β-CD from 890 to 1070 M^{-1}, in the presence of 0.25% (w/v) poly(vinylpyrrolidone). Further increases were also noted with methyl- and carboxy-methyl-β-CD derivatives.

3. Modifying drug release from polymeric matrices using cyclodextrin

3.1. Physical mixtures and drug-cyclodextrin complexes

3.1.1. Enhancing drug release

Cyclodextrins have the potential to enhance drug release from polymeric systems by increasing the concentration of diffusible species within the matrix. Guo and Cooklock (1995) used a range of additives including cyclodextrins to increase the solubility of the poorly water-soluble opioid analgesic, buprenorphine, and modify its release from buccal patches composed of poly(acrylic acid), poly(isobutylene) and poly(isoprene). They reported both α- and β-CD to be better solubilisers of buprenorphine base and its HCl salt than the bile salts, sodium taurocholate and sodium glycodeoxycholate, with β-CD yielding the greatest increase in solubility. Cumulative in vitro drug release from those patches containing a 1:1 drug:β-CD ratio was 50% after 24 h. This was more than twofold higher than a matrix containing drug alone at the same load. Samy and Safwat (1994) also used β-CD to alter the release rate of flurbiprofen, diclofenac sodium and piroxicam from silica (Aerosil®) and cellulosic based gels. Co-precipitates of the NSAID's with β-CD were prepared by evaporation of an aqueous-ethanolic equimolar solution of flurbiprofen or piroxicam and β-CD, or an aqueous equimolar solution of diclofenac sodium and β-CD. Infrared spectroscopy, X-ray diffractometry and differential scanning calorimetry were used to characterise the co-precipitates but no clear evidence was reported as to whether complexes or physical mixtures of drug and cyclodextrin were isolated. β-CD increased the release of piroxicam and diclofenac sodium from both methylcellulose and hydroxypropyl-methylcellulose gels. β-CD also enhanced the release of flurbiprofen from an Aerosil® gel compared to free drug. However, a decrease in release was observed when the flurbiprofen complex was formulated with the cellulosic gels. Importantly, flurbiprofen was completely dissolved in the cellulosic gels, but dispersed in the Aerosil®.

The observations of Guo and Cooklock (1995) and Samy and Safwat (1994) may be explained by a mechanistic approach to drug release from polymeric systems (Fig. 2). If solid drug exists within the hydrated matrix after equilibrium has been established between drug and cyclodextrin, then the presence of the cyclodextrin would not decrease the free concentration of drug in solution (as free drug in solution is also in equilibrium with drug in the solid state). In this instance, drug release would be the result of the combined diffusion of the free drug and the drug-β-CD complex

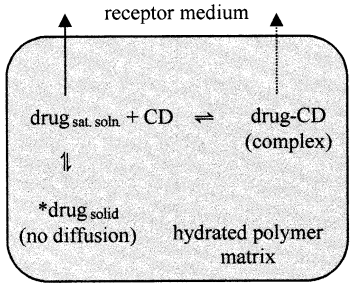

Fig. 2. Possible mechanism of drug release from a hydrated polymer matrix containing cyclodextrin and drug in a concentration in excess of its solubility. The model assumes both free and complexed drug are capable of diffusing from the matrix. An equilibrium exists between drug in the solid state, solubilised free drug and complex. *, If no solid drug is present the addition of cyclodextrin will decrease the free drug concentration.

(assuming diffusion of the complex was possible). Whilst the diffusivity of the drug-β-CD complex would be lower (due to its higher molecular weight), total drug release would be increased as the diffusion rates of free drug and drug-β-CD complex would be additive. This would explain the increased rates of release for buprenorphine and the NSAID's reported by Guo and Cooklock (1995) and Samy and Safwat (1994), respectively. If, however, the drug was present in concentrations below saturation, then the addition of β-CD would decrease the free drug concentration. This reduction in the free concentration of drug would result in a decrease in the diffusion rate of free drug, due to the reduction of its concentration gradient. Consequently, any observed reduction in drug release would be attributed to the difference in the diffusion coefficient between the free and complexed drug. The differential effect the incorporation of the β-CD-flurbiprofen complex had on drug release from the cellulosic and Aerosil® gels (Samy and Safwat, 1994), supports the mechanism proposed in Fig. 2. The ability of cyclodextrins to retard drug release through changes in drug solubility and diffusion coefficients will be discussed further in Section 3.1.2.

The addition of cyclodextrin to polymeric systems may also enhance drug release by acting as channelling or wicking agents or by promoting erosion of the matrix. Villar-López et al. (1999) evaluated the potential of β-CD to enhance the release of a glucocorticoid, triamcinolone acetonide, from pellets containing microcrystalline cellulose (MCC). Pellets containing 5:90:5 drug:β-CD:MCC demonstrated a near complete release of drug in phosphate buffer after 2 h. By comparison, pellets prepared with a 5:80:15 ratio released $< 60\%$, whilst pellets prepared without β-CD released $< 20\%$ of the glucocorticoid over the same time period. Scanning electron micrographs of all pellets after 5 h of dissolution testing showed an increased particle porosity in those pellets containing the cyclodextrin. In addition, β-CD readily formed an inclusion complex with triamcinolone acetonide ($K_{assoc} = 2800\ M^{-1}$), and a > 10-fold increase in drug solubility was observed upon the addition of 20 mM of β-CD. Thus, the enhanced release of drug was a result of the incorporated cyclodextrin dissolving upon contact with water, increasing the porosity of the matrix, but also allowing the removal of drug from the pellet via its inclusion within the β-CD cavity.

Other examples of using cyclodextrins to promote drug release through dissolution-erosion mechanisms are given by Giunchedi et al. (1994) and Song et al. (1997). Like Villar-López et al., both groups attributed an improved drug release to the ability of the incorporated cyclodextrin to both enhance the aqueous solubility of drug, whilst concomitantly acting as a water-leachable component and promoting matrix erosion.

The concept of using cyclodextrins to promote hydration of polymeric systems has been explored by a number of research groups. Gürsoy et al. (1995) exploited the ability of cyclodextrins to act as hydrating agents to accelerate the rate of release of dipyridamole from tabletted microspheres. β-CD was used as an additive during the compression of microspheres. β-CD promoted the diffusion of water into the tablet, resulting in enhanced drug release without tablet disintegration. Release of dipyridamole from these tabletted microspheres was faster than with no additive, but still sustained (70% at 5 h). It appears that this effect was not a consequence of complexation. The cyclodextrin was used as a wicking agent.

Finally, one of the few examples in which cyclodextrin was incorporated into microcapsules was described by Utsuki et al. (1996) and again highlighted the ability of cyclodextrin to promote hydration within polymeric carriers. In a procedure first described by Loftsson et al. (1992), they prepared microcapsules composed of ethylcellulose, HP-α-CD and the anti-cancer agent carboplatin. In vitro release studies showed an enhanced release of drug in microcapsules containing HP-α-CD compared to those containing drug alone (Fig. 3). This release corresponded with an increased hydration and swelling of these microcapsules. The therapeutic efficacy of the product for the treatment of brain tumour (glioma model) was investigated in rats. Animals receiving an intratumoral injection of microcapsules containing the carboplatin-HP-α-CD complex showed a median survival of 51 days, compared with microcapsules containing drug alone (34 days) and the control group (microcapsules only, 24 days). The microencapsulation of the carboplatin-HP-α-CD complex apparently protected the drug from decomposition and enhanced in vivo drug release following implantation, extending time of survival.

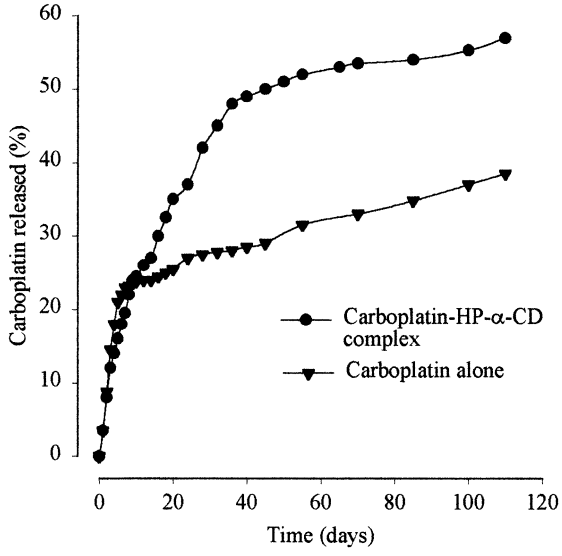

Fig. 3. Release profile of carboplatin from microcapsules containing carboplatin alone or a carboplatin-HP-α-CD complex, in unstirred 0.9% sodium chloride at 37°C (Utsuki et al. 1996; adapted with permission from Elsevier Science).

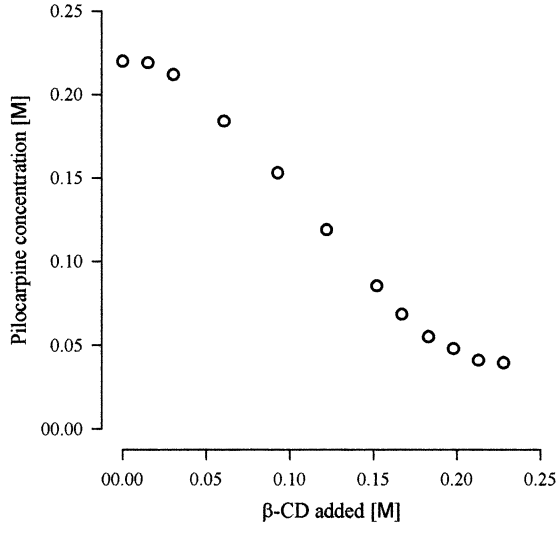

Fig. 4. Phase solubility profile of pilocarpine with β-CD in pH 8.0 buffer at 4°C (values represent means, $n = 2$; Davies et al., 1996).

3.1.2. Retarding drug release

We have previously described how reduced drug solubility and rates of dissolution in aqueous medium can be achieved through complexation with poorly water-soluble alkylated cyclodextrin derivatives (Section 1.2.2). Reduced solubility below that of the parent may also occur following complexation with β-CD, particularly for guests having good aqueous solubility. Such effects result in a type B phase-solubility diagram (Grant and Higuchi, 1990). An example of this is the complex formed between β-CD and pilocarpine (Fig. 4). Davies et al. (1996) used this pilocarpine-β-CD complex to control the release of drug from ophthalmic inserts prepared from a variety of polymers. In methylcellulose inserts, this poorly water-soluble complex significantly reduced the rate of drug release compared to inserts containing either free drug or a physical mixture of pilocarpine with β-CD (Fig. 5). In this instance, the incorporation of a poorly water-soluble complex into the polymer insert reduced the total concentration of diffusible species, resulting in a retarded release.

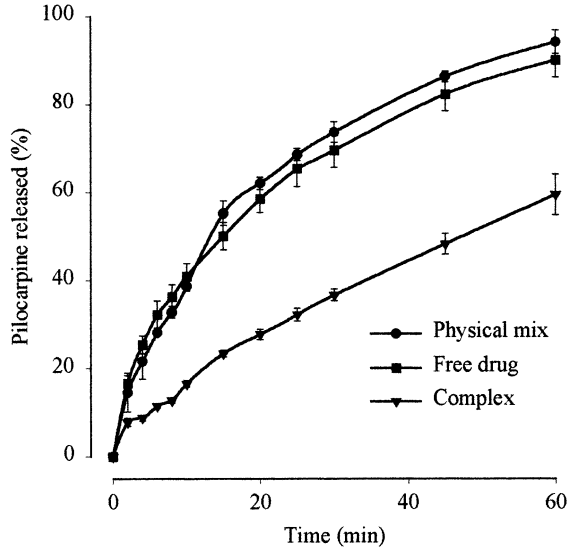

Fig. 5. Release profile of pilocarpine from methylcellulose inserts containing a physical mixture of pilocarpine and β-CD, drug alone or a pilocarpine-β-CD complex, in simulated tear solution at 33°C (mean ± SE $n = 4$; Davies et al., 1996).

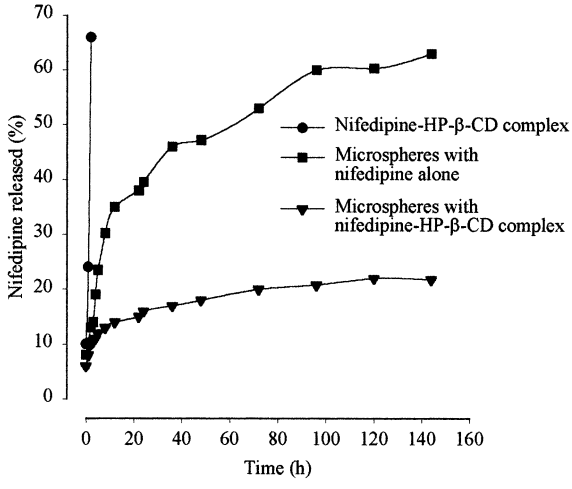

Fig. 6. Release profiles of nifedipine from chitosan microspheres in phosphate buffer (pH 7.4) at 37°C (mean, $n = 3$). Drug dissolution from a nifedipine-HP-β-CD complex alone is also shown for comparison (Filipović-Grčić et al., 1996; adapted with permission from Elsevier Science).

However, drug solubility is only one of the physicochemical parameters that can be altered by cyclodextrins. The diffusivity of drug molecules within a polymer matrix may also be lowered upon formation of a drug-cyclodextrin complex, as complexation can represent a 3–25-fold increase in molecular weight (Szejtli, 1988). We noted earlier (Fig. 2) that given solid drug exists within the matrix and a concomitant diffusion of the free and complexed drug forms occur, an increase in release may be possible. If however, diffusion of the drug complex is not possible, a retardation of drug release may be observed.

A restricted diffusion of the drug-cyclodextrin complex may explain the reduction in salicylic acid release observed by Sreenivasan (1997a) from a β-CD/poly(vinyl alcohol) (PVA) gel formulation. Cumulative release of the drug in water after 10 h approached 60% for PVA gel alone, compared to less than 20% in a gel containing 2.5:1 PVA:β-CD. This was despite a similar degree of swelling for both gels. No β-CD was detected in the release medium containing the PVA-β-CD gel.

Filipović-Grčić et al. (1996) also speculated that drug release from polymer matrices containing drug inclusion complexes may be retarded if diffusion of the cyclodextrin was not possible. Using cross-linked chitosan microspheres containing HP-β-CD, they demonstrated a reduced release in buffer of the poorly water-soluble drug nifedipine, compared to microspheres containing free drug (Fig. 6). This reduction occurred despite a near twofold increase in the aqueous solubility of nifedipine (from 5×10^{-6} M to 9.8×10^{-6} M) in the presence of 1×10^{-2} M HP-β-CD. Whilst the diffusion of the cyclodextrin molecule itself from the microspheres was considered unlikely, its release was not analysed. The authors proposed that during the release studies, nifedipine rapidly dissociated from the complex, resulting in an increased concentration of free cyclodextrin within the polymer matrix. A more hydrophilic, chitosan/cyclodextrin matrix was formed as a result, decreasing drug-matrix permeability and slowing the release of drug. Of note is that the microspheres were prepared using sunflower oil, whose lipid components have been shown to form strong complexes with cyclodextrins (Schlenk and Sand, 1961; Laurent et al., 1994; López-Nicolás et al., 1995). The competitive displacement of nifedipine from the cyclodextrin cavity by such residues is possible and consequently may have influenced drug release.

Examples thus far have demonstrated a number of modalities by which physically mixed and complexed cyclodextrins can modify drug release from polymeric delivery systems. Their incorporation into polymeric systems can affect the solubility or diffusivity of drug, improve hydration of the polymer matrix or promote its erosion. The effect on drug release of covalently binding cyclodextrins with polymer(s) shall now be considered.

3.2. Cyclodextrin-polymer conjugates and cross-linking agents

Cyclodextrins can be polymerised by themselves using only a cross-linking agent such as epichlorohydrin or by linking them to pre-existing polymers. Such materials have found a variety of applications in the industrial, food and pharmaceutical industries (Friedman, 1991). Silica-cyclodextrin conjugates, for example, have been particularly successful in both liquid and gas chromatography for the separation of chiral drugs (Duchêne, 1991; Pasutto, 1992).

Provided access to the cyclodextrin cavity is not obstructed, cyclodextrin-polymer conjugates can still form inclusion complexes, however their K_{assoc} is usually less than that noted for the free cyclodextrin (Szeman et al., 1987; Sreenivasan, 1997b,c).

Polymeric matrices containing conjugated cyclodextrins capable of forming inclusion complexes have the potential to modify drug release, though evidence in the literature is limited. Cyclodextrin conjugates are effectively immobilised within such matrices. Consequently, the diffusion of drug through such systems may be impeded if they form complexes with bound cyclodextrin. This principle has largely been investigated with respect to ionisable matices, where the release of oppositely charged drugs can be significantly slower (See et al., 1987; Peppas and Wright, 1998; Sriwongjanya and Bodmeier, 1998).

The potential for the sustained release of [^{3}H]-5-fluorouracil from a hydrogel composed of an α-CD/poly(acrylic acid) ester conjugate was investigated by Chino et al. (1992). Comparison of this product was then made with poly(acrylic acid) hydrogels containing physically mixed cyclodextrin (not covalently bound) or polymer alone. The time taken to achieve 50% release for the cyclodextrin-polymer conjugate hydrogel was 60% longer than that for the hydrogel containing poly(acrylic acid) alone. Notably, the hydrogel containing a corresponding physical mixture of cyclodextrin and polymer showed a comparable release rate to that of the conjugate, indicating a low diffusivity of the inclusion complex in this gel.

The use of cyclodextrins themselves as cross-linking agents for polymer matrices has been reported by a number of groups. Paradossi et al. (1997) formed a cross-linked chitosan-cyclodextrin hydrogel by reacting oxidised (polyaldehyde) β-CD with chitosan. ^{1}H-NMR studies showed a reduced mobility of water within this network, confirming the formation of a rigid cross-linked polymer mesh. A subsequent report (Crescenzi et al., 1997) reviewed the synthetic procedures for this and other carbohydrate-polymer networks. Specific pharmaceutical applications for these hydrogels were not discussed. García-González et al. (1993) studied the release of metoclopramide from poly(acrylic acid) matrices cross-linked with β-CD. Hydrogels composed of β-CD and poly(-acrylic acid) were prepared by heating at 90°C for 4 h. It was proposed that the primary hydroxyl groups of the cyclodextrin formed an ester cross-link with the carboxylic acid groups of the polymer, via a condensation reaction. The influence of both β-CD concentration (cross-linking agent) and molecular weight of the polymer on drug release was then investigated. Both the extent of hydrogel swelling and the rate of drug release was found to be affected by these two factors and the interaction between them. An increased cyclodextrin content resulted in a reduced level of hydrogel swelling and a reduced rate of drug release. This observation was attributed to increased cross-linking and a consequent reduction in mesh size. No comment was made on the role of complexation, if any, in retarding the release of drug from the gel. Importantly, Blanco-Fuente et al. (1996) speculated that the possibility of β-CD undergoing esterification with poly(acrylic acid) at these temperatures was unlikely, and proposed that acid anhydride formation within and between the polymer chains would be the predominant chemical reaction at temperatures between 90 and 130°C.

Bibby et al. (1998) also utilised the hydroxyl groups of β-CD to form an ester with the carboxylic acid groups of poly(acrylic acid). Microspheres were prepared through a water-in-oil solvent evaporation process in which β-CD and polymer were added to the aqueous phase prior to synthesis, and were of a suitable size for ocular/nasal administration (20–30 μm). Solid state ^{13}C-NMR studies suggested that in the presence of β-CD two concomitant reactions occurred during microsphere synthesis: esterification of the carboxylic acid groups of the poly(acrylic acid) with the hydroxyl group(s) of the carbohydrate *and* polymer acid anhydride formation (Bibby et al., 1999a). However, whether this covalently bound β-CD was attached to the polymer by a single hydroxyl group or was present as a cross-linker could not be determined. Subsequent studies (Bibby et al., 1999b) showed post-synthesis loading of these microspheres with phenolphthalein or rhodamine B was possible using saturated propan-2-ol solutions. These dyes were selected as model drugs as both are capable of forming complexes with β-CD. The presence of β-CD within the matrix, however, failed to modify the in vitro release of either dye. This was attributed to a number of factors including: a low degree of cross-linking within the matrix; the presence of oil contaminants and organic solvent residues perturbing the dye-β-CD complex, and; steric hindrance/conformational changes in the β-CD molecule reducing its ability to complex guests. Modification of the synthetic technique may overcome these limitations.

4. Summary

The incorporation of cyclodextrins into polymeric matrices can modify drug release by a variety of mechanisms.

Cyclodextrins can increase drug release by:

1. improving the aqueous solubility of drugs,
2. acting as channelling agents and promoting erosion of the matrix,
3. acting as wicking agents, or
4. increasing the concentration of diffusible species (provided solid drug exists within the matrix and diffusion of both free and complexed drug is possible).

Adding cyclodextrins to polymeric matrices can reduce drug release by:

1. complexing drug, effectively increasing its molecular weight and hence reducing its diffusivity (provided no excess drug is present),
2. reducing the concentration of diffusible species by forming poorly soluble complexes,
3. reducing the concentration of diffusible species by forming drug-cyclodextrin complexes in which the host is covalently bound to the polymer backbone, or
4. acting as cross-linking agents and decreasing polymer mesh size.

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