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Research paper

Effect of SBE7-β-cyclodextrin complexation on carbamazepine release from sustained release beads

J.S. Smith[a,*], R.J. MacRae[a], M.J. Snowden[b]

[a]Pharmaceutical Research and Development, Pfizer Global Research and Development, Sandwich, UK
[b]Medway Sciences, University of Greenwich, Chatham, UK

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Abstract

The effect of SBE7-β-cyclodextrin together with hydroxypropylmethyl cellulose (HPMC) or polyvinylpyrrolidone (PVP) on the saturated solubility and delivery of carbamazepine (a poorly soluble drug) from sustained release (SR) beads was investigated. Carbamazepine solubility at room temperature increased from 0.1 to 5.4 mg/ml by forming an inclusion complex with SBE7-β-cyclodextrin (15%w/v). HPMC (0.1%w/v) also increased the aqueous solubility of carbamazepine, acting both alone and synergistically with SBE7-β-cyclodextrin, to produce solubility values of 0.26 and 8.1 mg/ml respectively. PVP (0.1–0.5%w/v) had no effect on carbamazepine solubility, either alone or in combination with SBE7-β-cyclodextrin. The addition of SBE7-β-cyclodextrin to SR beads increased the rate of carbamazepine release. In addition, comparable release rates where obtained when lower ratios of SBE7-β-cyclodextrin together HPMC were incorporated in the SR bead. Therefore this ternary drug cyclodextrin polymer system was considered preferable over the binary drug cyclodextrin system for SR beads, as less cyclodextrin was required. However, both binary and ternary approaches were considered suitable techniques to improve the release rate and potentially the in vivo bioavailability of poorly soluble drugs that had previously exhibited slow or incomplete release from SR beads.

Keywords: Beads; Carbamazepine; Cyclodextrin; Hydroxypropyl methylcellulose; Sustained release

1. Introduction

Multiparticulate dosage forms are popular for the sustained release (SR) delivery of drugs, having reproducible upper gastrointestinal tract transit and minimal risk of dose dumping in vivo when compared to alternative SR formulations [1]. Encapsulated multiparticulate devices contain drug loaded beads, ~1 mm in diameter, each coated with a SR polymeric membrane such as ethylcellulose or an acrylic copolymer [2–5]. Drug delivery from these SR beads is dependent on the rate of drug release through the membrane, and therefore drug solubility and dissolution within the bead. Drugs with poor aqueous solubility can exhibit slow or incomplete release from SR beads, resulting in poor in vivo bioavailability, unless the drug release rate through the membrane can be suitably enhanced. Thus, materials that increase drug solubility within the bead and enhance the rate of drug release are of great interest and importance when developing a sustained release dosage form for a poorly soluble drug. Therefore, this study has been designed to investigate the solubility-enhancing potential of sulphobutyl ether-β-cyclodextrin [6] to improve the delivery of a poorly soluble model drug from SR beads.

Cyclodextrins are capable of forming an inclusion complex with many drugs. This can result in improved chemical stability, an increase in the apparent aqueous solubility, and higher bioavailability for many drugs [7–10]. Cyclodextrins are a group of cylindrical cone shaped cyclic oligosaccarides having a lipophilic central cavity and hydrophilic outer surface. There are 3 main parent cyclodextrins, alpha (α-cyclodextrin), beta (β-cyclodextrin,), and gamma (γ-cyclodextrin), which contain 6, 7, and 8,

* Corresponding author. Pharmaceutical Research and Development, Pfizer Global Research and Development, Sandwich, Kent CT 13 9NJ, UK. Tel.: +44 1304 643964; fax: +44 1304 640544.
E-mail address: janet.s.smith@pfizer.com (J.S. Smith).

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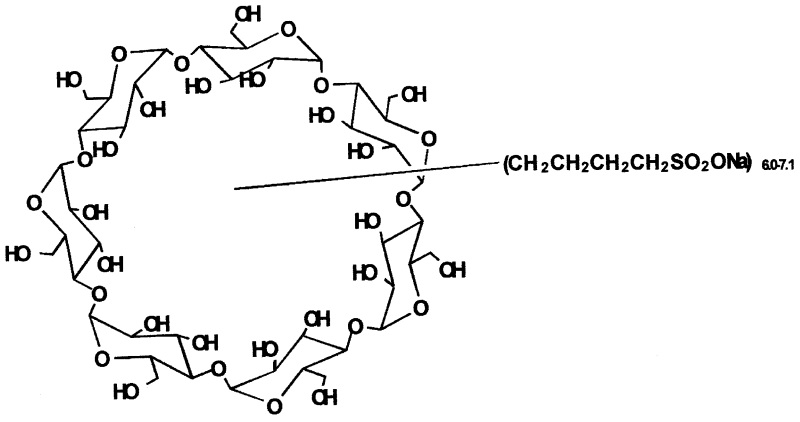

Fig. 1. Chemical structure of SBE7-β-cyclodextrin.

glucopyranose units respectively. Due to cavity size, β-cyclodextrin is considered the most suitable for pharmaceutical drug complexation, but it is poorly soluble [7]. The amorphous derivative hydroxypropyl-β-cyclodextrin has a solubility of >600 mg/ml [8]. However, in this study another β-cyclodextrin derivative with good solubility and potentially a greater affinity for complexation [11] will be investigated, sulphobutyl ether-β-cyclodextrin (SBE7-β-cyclodextrin), see Fig. 1. This is a sulphobutyl ether, sodium salt, derivative of β-cyclodextrin, with an average degree of substitution of 6.5 [11].

The efficiency of complexation between cyclodextrin and drug is often low, requiring high levels of cyclodextrin to suitably increase the solubility of certain drugs in aqueous media. However, it is known that water soluble polymers such as hydroxypropylmethyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) can interact with poorly soluble drugs, leading to an increase in the drug solubility in conventional aqueous media and cyclodextrin solutions [7,12–16]. As this technique has the ability to further increase drug solubility, the potential of small quantities of HPMC and PVP with SBE7-β-cyclodextrin will be investigated in this study.

Carbamazepine is ideal as a model compound for poorly soluble drugs, see Fig. 2. It has an aqueous solubility of 0.1 mg/ml, and is known to complex with cyclodextrins including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and γ-cyclodextrin [13,17]. Though few reports have been published on SBE7-β-cyclodextrin carbamazepine interactions, carbamazepine solubility was reported to increase to 0.8 mg/ml in the presence of SBE7-β-cyclodextrin (15 mg/ml) [18]. The interaction between carbamazepine and cyclodextrins is reported to be a 1:1 inclusion complex [17,19,20]. Hydroxypropyl-β-cyclodextrin is reported to have superior carbamazepine solubilising ability than α-cyclodextrin and β-cyclodextrin [17]. Therefore, in this study carbamazepine solubility data generated with SBE7-β-cyclodextrin will be compared to literature values for hydroxypropyl-β-cyclodextrin.

In summary, the aim of this study was to assess the potential of SBE7-β-cyclodextrin together with HPMC or PVP to solubilise and deliver the poorly soluble model drug carbamazepine from SR beads. Initial experiments focussed on the ability of SBE7-β-cyclodextrin, HPMC and PVP to complex and solubilise carbamazepine.

2. Materials and methods

2.1. Materials

Surelease® (E-7-19010), an aqueous ethylcellulose dispersion, and HPMC (Methocel® E5) were obtained from Colorcon (UK), PVP (Kollidon® K30) from BASF PLC (UK), and sugar spheres (14–18 mesh) from Mendell (UK). Carbamazepine (99%) was purchased from Aldrich (UK), and SBE7-β-cyclodextrin was obtained from Pfizer Global Research and Development (UK).

2.2. Carbamazepine analysis

Quantitative UV spectrophotometry (Kontron Uvikon 931 spectrophotometer) was performed at the λ_{max} of 285 nm, following sample dilution in water.

2.3. Carbamazepine saturated solubility studies

Aqueous solutions were prepared containing SBE7-β-cyclodextrin (0, 5, 10, and 15% w/v) and PVP (0, 0.1, 0.25,

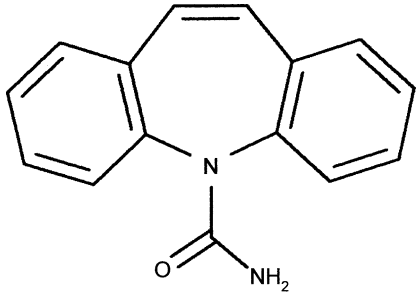

Fig. 2. Chemical structure of carbamazepine.

and 0.5% w/v) or HPMC (0, 0.1, 0.25, and 0.5% w/v). To 5 ml of each solution, 100 mg of carbamazepine was added and left to mix for 3 days at ambient conditions of temperature and humidity on a tumbling mixer prior to filtration and carbamazepine analysis. Samples were also left to mix for 1, 3 and 7 days prior to analysis and confirmed solubility equilibration had been reached at 3 days.

The equilibrium constants of carbamazepine SBE7-β-cyclodextrin inclusion complexes were determined from the phase-solubility diagrams according to Higuchi and Connor [21] by plotting carbamazepine molar solubility on the vertical axis, against SBE7-β-cyclodextrin molar concentration, for each concentration of polymer. As the slope of these diagrams was <1, it was assumed that a 1:1 stoichiometric complex was formed. The apparent equilibrium constants ($K_{1:1}$) were then determined from Eq. (1) [21].

$$K1:1 = \frac{\text{slope}}{D_0(1 - \text{slope})} \quad (1)$$

D_0, solubility of carbamazepine without cyclodextrin present; Slope, slope of phase-solubility diagram [21].

2.4. Preparation of SR beads

Aqueous binary solutions were prepared containing a ratio of SBE7-β-cyclodextrin (400): carbamazepine (4, 8, or 12). Aqueous ternary solutions were prepared containing a ratio of SBE7-β-cyclodextrin (400): carbamazepine (8, 12, 16, or 20): HPMC (4). All aqueous solutions had a final solids content of 10%w/v. Solutions were sprayed onto sugar spheres to obtain a 30% weight gain, using an Aeromatic fluid bed Aerocoater unit (size 1), set to 1.2 bar atomisation pressure and 65 °C exhaust air temperature. In addition, a control carbamazepine ethanolic solution (2%w/v) was prepared and sprayed onto sugar spheres to obtain a 2% weight gain, using settings of 1.0 bar atomisation pressure and 50 °C exhaust air temperature.

All carbamazepine loaded beads were coated with a Surelease® dispersion (15% w/v solids) to obtain a 10% weight gain, using an exhaust air temperature of 60 °C, and then cured at 60 °C for 18 h.

Beads were assayed for carbamazepine content. Extraction was performed by sonicating beads in ethanol, diluting with water, further sonication, and mixing overnight prior to UV analysis. Scanning electron microscope techniques were employed to ensure reproducible coat thickness between batches.

2.5. Dissolution of carbamazepine from SR beads

The dissolution rate of carbamazepine from SR beads was monitored using automated dissolution apparatus consisting of IDIS EE software (Icalis Data Systems), dissolution bath (Vankel VK7000), peristaltic pump (PCP490, Icalis Data Systems), and UV spectrophotometry (see Section 2.2) with 5 cm pathlength cells. USP apparatus I (baskets, 100 rpm) was used to dissolute beads containing 4 mg carbamazepine in 900 ml media at 37 °C. Mean data ($n=6$), with minimum and maximum values as error bars were plotted. The majority of dissolution testing was performed in water, however pH 2 media (0.01 M HCl, 0.12 M NaCl) and pH 7.5 media (0.064 M KCl, 0.035 M NaCl, 0.006 M KH_2PO_4, 0.0005 M NaOH) were initially used to simulate physiological conditions in the gastrointestinal tract.

2.6. Dissolution of SBE7-β-cyclodextrin from SR Beads

The dissolution rate of SBE7-β-cyclodextrin from SR beads was determined using a dissolution bath (Vankel VK7000) with manual sampling at known time points ($n=2$). USP apparatus I (baskets, 100 rpm) was used to dissolute beads containing 1 g SBE7-β-cyclodextrin in 500 ml water at 37 °C. Quantitative SBE7-β-cyclodextrin analysis was performed by HPLC using a refractive index detector.

3. Results and discussion

3.1. Carbamazepine saturated solubility study

The saturated solubility of carbamazepine was shown to increase with increasing SBE7-β-cyclodextrin concentration, indicating that some degree of complexation was taking place between these two materials, see Tables 1 and 2. This was supported by additional (unpublished) studies on dried material using powder X-ray diffraction, which showed amorphous carbamazepine and therefore potentially complexed material had been formed.

Table 1
Carbamazepine saturated solubility (mg/ml) with SBE7-β-cyclodextrin and HPMC ($n=1$)

HPMC, %w/v (mmol/l)	SBE7-β-cyclodextrin			
	0%w/v (0 mol/l)	5%w/v (0.023 mol/l)	10%w/v (0.046 mol/l)	15%w/v (0.069 mol/l)
0 (0)	0.11 (0.47 mmol/l)	1.71 (7.24 mmol/l)	3.51 (14.85 mmol/l)	5.43 (22.98 mmol/l)
0.10 (0.050)	0.26 (1.10 mmol/l)	2.78 (11.76 mmol/l)	5.36 (22.68 mmol/l)	8.13 (34.41 mmol/l)
0.25 (0.125)	0.26 (1.10 mmol/l)	2.83 (11.98 mmol/l)	5.36 (22.68 mmol/l)	8.15 (34.49 mmol/l)
0.50 (0.250)	0.26 (1.10 mmol/l)	2.75 (11.64 mmol/l)	5.26 (22.26 mmol/l)	8.00 (33.86 mmol/l)

Table 2
Carbamazepine saturated solubility (mg/ml) with SBE7-β-cyclodextrin and PVP ($n=1$)

PVP, %w/v (mmol/l)	SBE7-β-cyclodextrin			
	0%w/v (0 mol/l)	5%w/v (0.023 mol/l)	10%w/v (0.046 mol/l)	15%w/v (0.069 mol/l)
0 (0)	0.11 (0.47 mmol/l)	1.71 (7.24 mmol/l)	3.51 (14.85 mmol/l)	5.43 (22.98 mmol/l)
0.10 (0.02)	0.11 (0.47 mmol/l)	1.69 (7.15 mmol/l)	3.36 (14.22 mmol/l)	5.28 (22.34 mmol/l)
0.25 (0.05)	0.12 (0.51 mmol/l)	1.69 (7.15 mmol/l)	3.47 (14.68 mmol/l)	5.26 (22.26 mmol/l)
0.50 (0.10)	0.13 (0.55 mmol/l)	1.76 (7.45 mmol/l)	3.40 (14.39 mmol/l)	5.45 (23.06 mmol/l)

The addition of 0.1%w/v HPMC to water (in the absence SBE7-β-cyclodextrin) also enhanced carbamazepine solubility, suggesting that an interaction was taking place between these two materials, see Table 1. Katzhendler et al. [16] reported an interaction between these two materials in solution, and assumed this occurred by hydrogen bonding. At HPMC levels of 0.2% and 0.5% (w/v), carbamazepine solubility is similar to that observed in 0.1% HPMC (w/v), see Table 1. Similar observations have been reported by Loftsson et al. [15].

The saturated solubility of carbamazepine increased from 0.11 to 0.26 and 3.51 mg/ml, by the addition of HPMC (0.1%w/v) and SBE7-β-cyclodextrin (10%w/v) respectively, see Table 1. However a solubility value of 5.36 mg/ml was observed when HPMC (0.1%w/v) and SBE7-β-cyclodextrin (10%w/v) were combined. This synergistic improvement in carbamazepine solubility, is considered to be due to HPMC increasing the concentration of free carbamazepine available in solution to interact with the SBE7-β-cyclodextrin. As the SBE7-β-cyclodextrin carbamazepine complex and free carbamazepine are in equilibrium, a rise in the free carbamazepine concentration may be expected to lead to an increase in the levels of complexed material. Hence a synergistic improvement in carbamazepine solubility will occur. However, although the carbamazepine solubility increased in the presence of HPMC and SBE7-β-cyclodextrin, a reduction in the apparent equilibrium constant ($K_{1:1}$) was observed as the level of HPMC increased, thereby revealing a reduction in the complexation efficiency of the SBE7-β-cyclodextrin. This observation differs to the increase in $K_{1:1}$ observed by Loftsson et al. [13] when adding HPMC to various drugs with hydroxypropyl-β-cyclodextrin.

In contrast to HPMC, carbamazepine solubility was not significantly affected by the addition of PVP at levels of 0.1–0.5% (w/v), either with or without SBE7-β-cyclodextrin, see Table 2. Therefore, in this case, PVP does not affect the solubility of free carbamazepine and no synergistic improvement in solubility is observed when SBE7-β-cyclodextrin and PVP are combined. This supports the hypothesis that water soluble polymers may increase the solubility of cyclodextrin drug systems by increasing the concentration of free drug in solution.

3.2. Phase solubility and equilibrium constants

Graphical representation of the carbamazepine solubility data, using molarity values, reveals a linear increase in carbamazepine solubility with a rise in SBE7-β-cyclodextrin concentration, both in the presence and absence of PVP or HPMC, see Fig. 3. These Type A_L phase solubility diagrams [21] typically have a slope <1. Therefore it is a reasonable assumption that 1:1 stoichiometry exists and an apparent equilibrium constant ($K_{1:1}$) can be used to describe this system [21], concurrent with the previously reported 1:1 complexation of carbamazepine and hydroxypropyl-β-cyclodextrin [19].

The range of $K_{1:1}$ values observed between 809 and 1035 (see Table 3) compare favourably to the value of 600 reported for carbamazepine and hydroxypropyl-β-cyclodextrin [19], indicating SBE7-β-cyclodextrin has a superior carbamazepine complexation efficiency. This may potentially be due to carbamazepine interacting with the anionically charged moiety of the SBE7-β-cyclodextrin. Superior cyclodextrin complexation efficiency may prove advantageous during dosage form design, and would therefore appear to be a potential advantage for SBE7-β-cyclodextrin.

Interestingly, though the solubility of carbamazepine was not significantly affected by the presence of PVP, the $K_{1:1}$ values show a trend to decrease in value with increasing

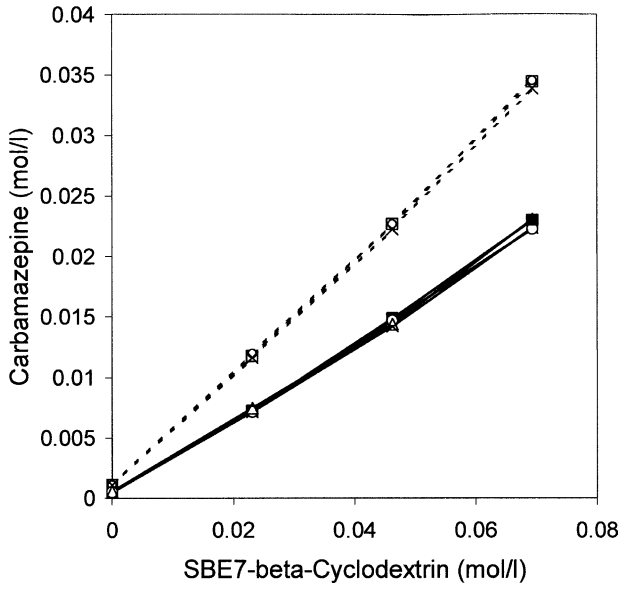

Fig. 3. Phase solubility diagram of carbamazepine with SBE7-β-cyclodextrin alone (- -■- -), and with 0.05 mmol/l HPMC (- -□- -), 0.125 mmol/l HPMC (- -○- -), 0.5 mmol/l HPMC (- -×- -), 0.02 mmol/l PVP (—×—), 0.05 mmol/l PVP (—○—), and 0.1 mmol/l PVP (—△—).

Table 3
The effect of PVP and HPMC on the apparent equilibrium constant ($K_{1:1}$) for the complexation between carbamazepine and SBE7-β-cyclodextrin ($n=1$)

Polymer (%w/v)	$K_{1:1}$ (l/mol)
None	1035
PVP:	
0.1	986
0.25	905
0.5	864
HPMC:	
0.1	837
0.25	838
0.5	809

PVP content. This is considered to be due to the very slight increase in carbamazepine solubility with increasing levels of PVP (without SBE7-β-cyclodextrin), as these solubility values (D_0) are used in the calculation of $K_{1:1}$, see Eq. (1).

3.3. Drug release

Carbamazepine solubility was observed to increase proportionally with SBE7-β-cyclodextrin concentration (refer to Section 3.1). Weight ratios were calculated from these solubility values to give a SBE7-β-cyclodextrin:carbamazepine ratio of 400:14, and a SBE7-β-cyclodextrin:-carbamazepine:HPMC ratio of 400:22:4. The latter ratio was determined from studies performed with 0.1%w/v HPMC, as HPMC levels above this did not further enhance carbamazepine solubility. These ratios support the maximum working carbamazepine ratio that permits all the carbamazepine to be in solution, assuming conditions are like those in the phase solubility analysis. SR beads were manufactured at a range of ratios below these carbamazepine maxima (as detailed in Section 2.4), to assess the effect of SBE7-β-cyclodextrin on carbamazepine delivery from SR beads.

Dissolution profiling reveals that SR beads containing carbamazepine and SBE7-β-cyclodextrin:carbamazepine (400:12) release 50% of carbamazepine in 12.5 and 3 h, respectively, see Fig. 4. This indicates a significant increase in the rate of carbamazepine release in the presence of SBE7-β-cyclodextrin. It is hypothesised that this is due to two main factors. The first factor being the increased solubility of carbamazepine in the presence of SBE7-β-cyclodextrin, as reported earlier in this study, which enables a more concentrated carbamazepine solution to occur within the bead, so increasing transport from the device. Enhanced carbamazepine wettability and rate of dissolution has previously been reported with α-cyclodextrin, β-cyclodextrin and hydroxypropyl-β-cyclodextrin [17,20]. The second factor that accounts for the increase in carbamazepine release rate is an increase in osmotic pressure within the bead, due to the osmotic effect of SBE7-β-cyclodextrin [1,22–24].

Carbamazepine delivery from SR bead formulations remained comparable in the various media evaluated, see Fig. 4, thereby endorsing the use of water as the media of choice for all latter dissolution studies. The zero order profile obtained for SR beads containing carbamazepine alone suggests the solution in the core is saturated with drug, so maintaining the concentration gradient that drives diffusional release. On the other hand, the first order profile obtained for the SR beads containing SBE7-β-cyclodextrin suggests the solution in the core is not saturated with either carbamazepine or cyclodextrin, due to good material solubility. As the solution concentrations fall, over a period of time, so does the concentration gradient that drives diffusional and osmotic release mechanisms, resulting in a first order release profile.

Within the range of SBE7-β-cyclodextrin:carbamazepine ratios examined (400:4–400:12), carbamazepine

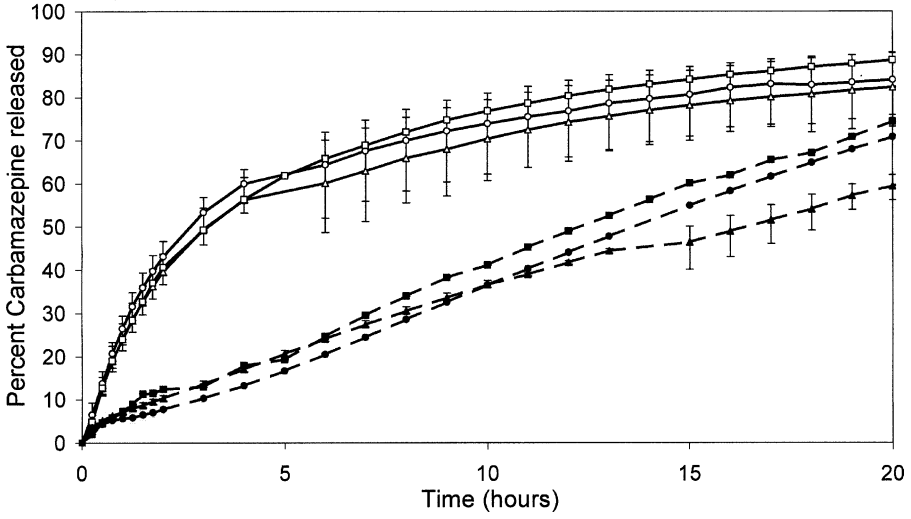

Fig. 4. Carbamamazepine release from SR beads containing carbamazepine, in water (–■–), pH2 (–●–), and pH7.5 (–▲–), and from SR Beads containing SBE7-β-cyclodextrin:carbamazepine (400:12), in water (—□—), pH2 (—△—), and pH7.5 (—○—).

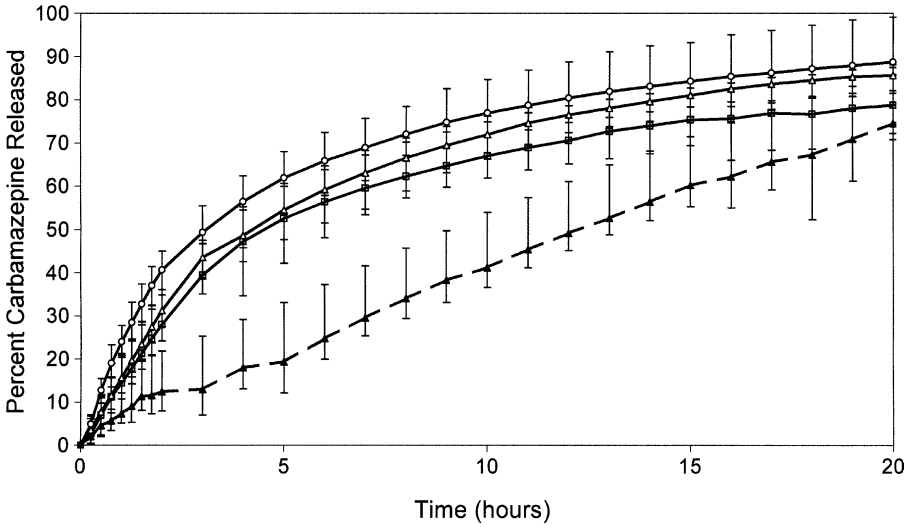

Fig. 5. Carbamazepine release from SR beads containing carbamazepine (–▲–), or SBE7-β-cyclodextrin: carbamazepine at a ratio of 400:4 (—△—), 400:8 (—□—), and 400:12 (—○—).

delivery appears comparable, see Fig. 5. This similarity was also observed for SR beads containing the various ratios of SBE7-β-cyclodextrin:carbamazepine:HPMC (400:8:4–400:20:4), see Fig. 6. This suggests that even at the maximum carbamazepine ratio, the SBE7-β-cyclodextrin content within the bead is not exhausted during the period of carbamazepine release. Therefore it was considered that SBE7-β-cyclodextrin may either be retained in the bead, unable to escape, or transported through the SR membrane at a similar or slower rate as carbamazepine. Thus studies were conducted to define the SBE7-β-cyclodextrin release rate (Section 3.4).

The use of SBE7-β-cyclodextrin to increase the rate of carbamazepine release from SR beads facilitates greater flexibility in the formulation design process. Enabling a range of desired release profiles to be obtained by modifying the SR bead coat composition and thickness [5]. Therefore it is considered that SBE7-β-cyclodextrin has the potential to improve drug delivery and in vivo bioavailability of other poorly soluble drugs from SR beads, which had previously exhibited slow or incomplete release.

The use of HPMC to form a ternary system with carbamazepine and SBE7-β-cyclodextrin had no effect on the carbamazepine release rate from SR beads, see Fig. 7. This suggests that the release rate is not sensitive to the small increase in carbamazepine solubility in the presence of HPMC. However, as HPMC increases the solubility of carbamazepine in the presence of SBE7-β-cyclodextrin it facilitates a lower SBE7-β-cyclodextrin ratio to be used in the SR bead, whilst maintaining a carbamazepine release rate equivalent to that of the binary system. This enables the SBE7-β-cyclodextrin:carbamazepine ratio of 400:12

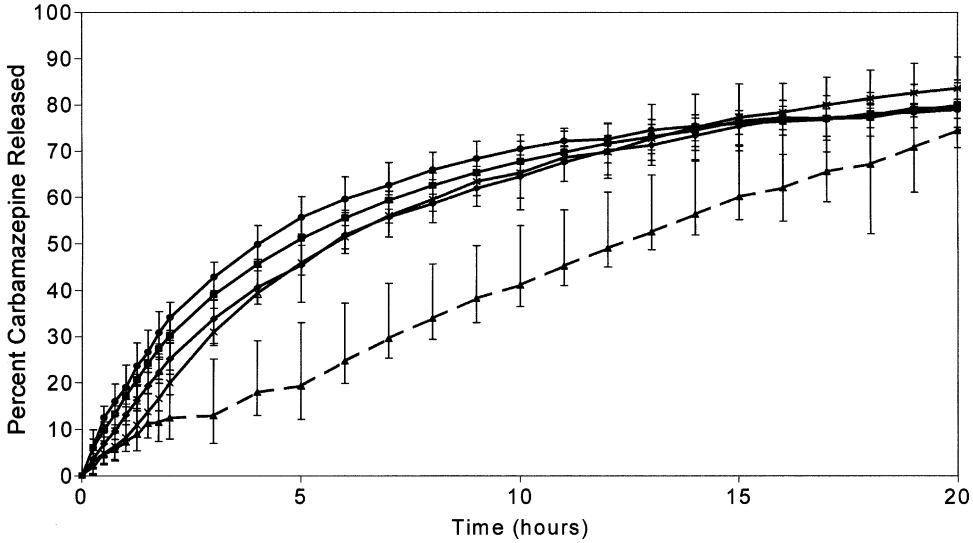

Fig. 6. Carmamazepine release from SR beads containing carbamazepine (–▲–), or SBE7-β-cyclodextrin:carbamazepine:HPMC at a ratio of 400:8:4 (—■—), 400:12:4 (—●—), 400:16:4 (—♦—), and 400:20:4 (—×—).

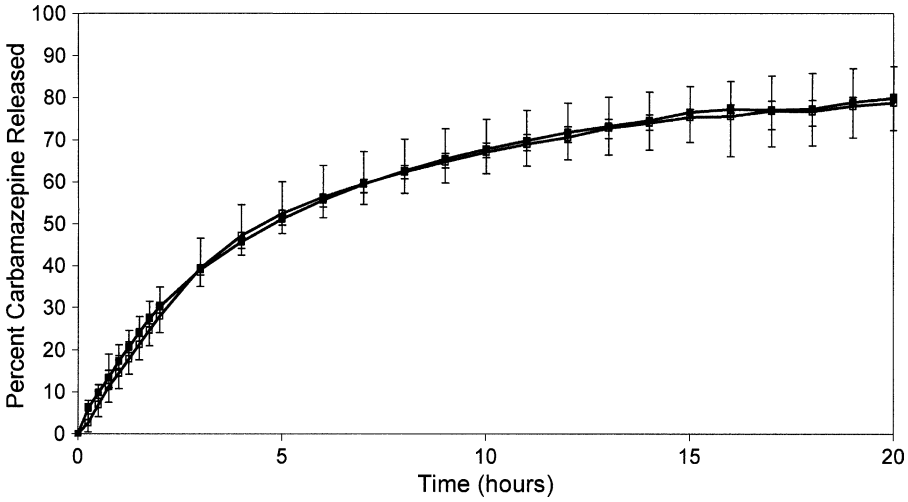

Fig. 7. Carbamazepine release from SR beads containing SBE7-β-cyclodextrin:Carbamazepine (400:8) (—□—), and SBE7-β-cyclodextrin:carbamazepine:HPMC (400:8:4) (—■—).

to be replaced with the SBE7-β-cyclodextrin:carbamazepine:HPMC ratio of 400:20:4, as detailed in Figs. 5 and 6. This ternary approach may therefore be advantageous over the drug cyclodextrin system in the formulation of SR beads of poorly soluble drugs, as the minimal use of cyclodextrin is beneficial from both a processing and cost perspective.

3.4. SBE7-β-cyclodextrin release

To assist in identifying the nature of carbamazepine release, quantitative SBE7-β-cyclodextrin analysis was performed during the dissolution of SR beads containing SBE7-β-cyclodextrin:carbamazepine complex (400:12). Graphical representation of the data demonstrates that the rate of SBE7-β-cyclodextrin release is similar to that of carbamazepine, see Fig. 8. It is therefore postulated that the free and complexed SBE7-β-cyclodextrin and carbamazepine remain in equilibrium while transporting across the membrane. The various mechanisms of drug release through such an ethylcellulose based pseudolatex membrane include diffusion through polymer and aqueous pores together with osmotically driven release through aqueous pores [1]. At membrane levels similar to those used in this study, numerous pores were reported to be present through which dissolution fluid can enter and dissolved drug exit [25]. Therefore, it is suggested that the main mechanism of carbamazepine transport from the SR beads containing carbamazepine alone, is diffusional release through the aqueous pores of the membrane. Whilst the major mechanisms of transport from the SR beads containing SBE7-β-cyclodextrin, are diffusion and osmotically driven release through the aqueous pores of the membrane, for both the free and complexed SBE7-β-cyclodextrin and carbamazepine. In this system, the SBE7-β-cyclodextrin is believed to enhance carbamazepine delivery by improving solubility and hence diffusion, whilst also increasing the osmotic drive.

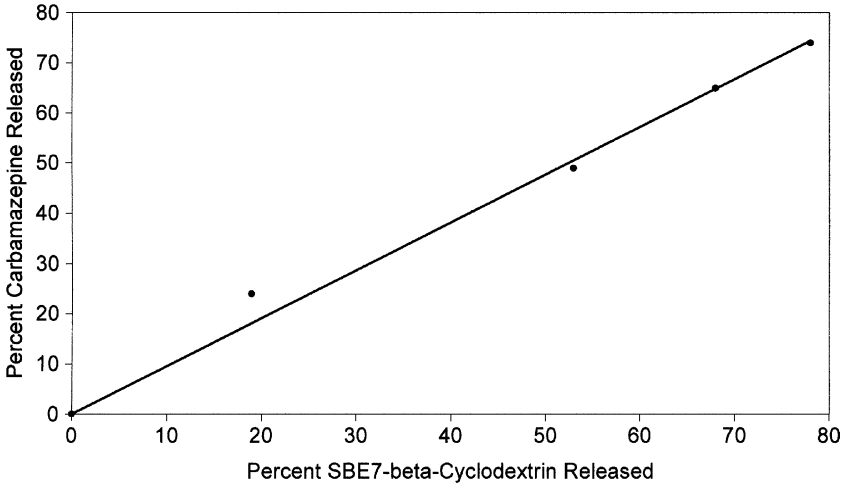

Fig. 8. Comparison of carbamazepine and SBE7-β-cyclodextrin release from SR beads containing SBE7-β-cyclodextrin:carbamazepine (400:12).

4. Conclusions

SBE7-β-cyclodextrin increases the aqueous solubility of carbamazepine by forming an inclusion complex that has a higher apparent equilibrium constant than that reported for hydroxypropyl-β-cyclodextrin. HPMC, but not PVP, increases the aqueous solubility of carbamazepine, acting both alone and synergistically with SBE7-β-cyclodextrin. Within a SR bead, SBE7-β-cyclodextrin increases the carbamazepine release rate, potentially by enhancing solubility and hence diffusion, whilst also increasing the osmotic drive through the Surelease® aqueous pores. SBE7-β-cyclodextrin has a similar release rate to carbamazepine, suggesting both free and complexed SBE7-β-cyclodextrin and carbamazepine transport across the membrane. The addition of HPMC does not improve the rate of carbamazepine release, but does reduce the ratio of SBE7-β-cyclodextrin needed to deliver carbamazepine and therefore has potential advantages over the binary system. Both binary and ternary approaches are considered as suitable techniques to potentially improve the delivery and in vivo bioavailability of poorly soluble drugs, which have previously exhibited slow or incomplete release from SR beads.

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