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The Pharmaceutical Use of Captisol®: Some Surprising Observations

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Abstract

The purpose of this paper is to share some recent observations on the pharmaceutical uses and properties of Captisol® or SBE_{7M}-β-CD in controlled porosity osmotic pump tablets (CP-OPT) and the underlying mechanism/s that lead to apparent zero-order drug release pattern. It would have been simple to attribute the apparent zero-order release mechanism/s of poorly water-soluble drugs from CP-OPTs and pellets utilizing Captisol® as both a solubilizing and osmotic agent, to purely osmotic and diffusional components. However, the mechanism may be more related to a counterbalancing of physical properties as the concentration of Captisol® changes within the matrix. Specifically, the initial concentration of Captisol® within a core is 0.3–0.4M. When this drops to lower values an osmotic pressure drop occurs across the membrane. Therefore, drug release should not follow apparent zero-order kinetics if all the drug is solubilized. However, as the viscosity within the tablet also drops, the apparent diffusion coefficient of both Captisol® and drug increases. Therefore, it appears that there is an initial resistance (hydraulic pressure) to fluid flow from the tablet through the rate-limiting microporous membrane. This resistance decreases so that even as osmotic pressure and concentration differences drop with time, counterbalancing faster release occurs. Osmotic driving force appears to be the most important initial driving force but a diffusional component becomes more significant with time.

Introduction

An illustration of the controlled porosity osmotic pump tablet (CP-OPT) concept is shown in Scheme 1. CP-OPTs were developed in the 1980's by Zentner et al. [1–3] for oral controlled drug delivery of reasonably water-soluble drugs. The device consisted of a tablet core containing a water-soluble drug, some osmotically active agents as well as other excipients, coated with a controlled porosity membrane. This membrane is mainly composed of a semipermeable, water-insoluble polymer and a pH-insensitive water-soluble pore forming additive, or "pore former" as well as a plasticizer. Upon administration, water is imbibed through the semipermeable polymer, also dissolving the pore former. A microporous membrane is thus formed *in situ*; its permeability depends on the coating formulation. The tablet core dissolves and the drug is released in a zero-order fashion due to the constant difference in pressure and concentration across the membrane. Zentner et al., described the release process by Equation (1), developed earlier by Theeuwes [4].

$$\frac{dM_t}{dt} = \frac{AS}{h} L_P \sigma \Delta\Pi + \frac{ADKS}{h}, \qquad (1)$$

where (dM_t/d_t) is the drug release rate, A, h, L_P and σ are the membrane surface area, thickness, hydraulic conductivity and reflection coefficient, respectively, S is the drug saturation solubility, $\Delta\Pi$ is the difference in osmotic pressure (OP) across the membrane, D is the drug diffusion coefficient across the membrane and K is the partition

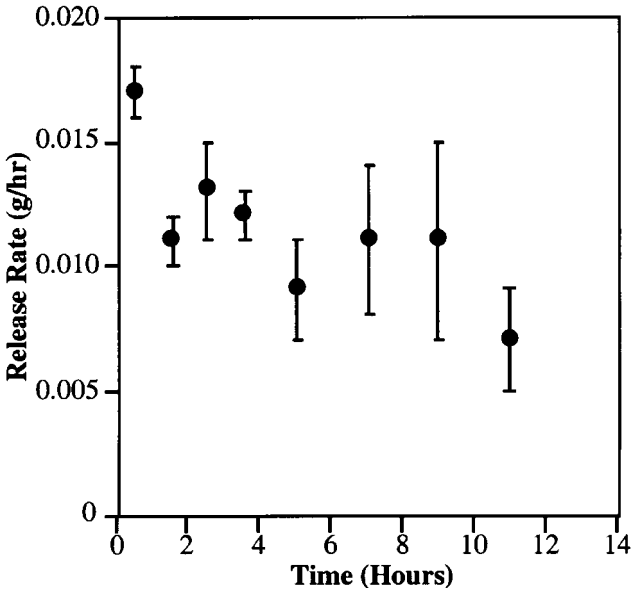

Figure 1. Scheme showing the principles of the controlled porosity osmotic pump tablet (CP-OPT).

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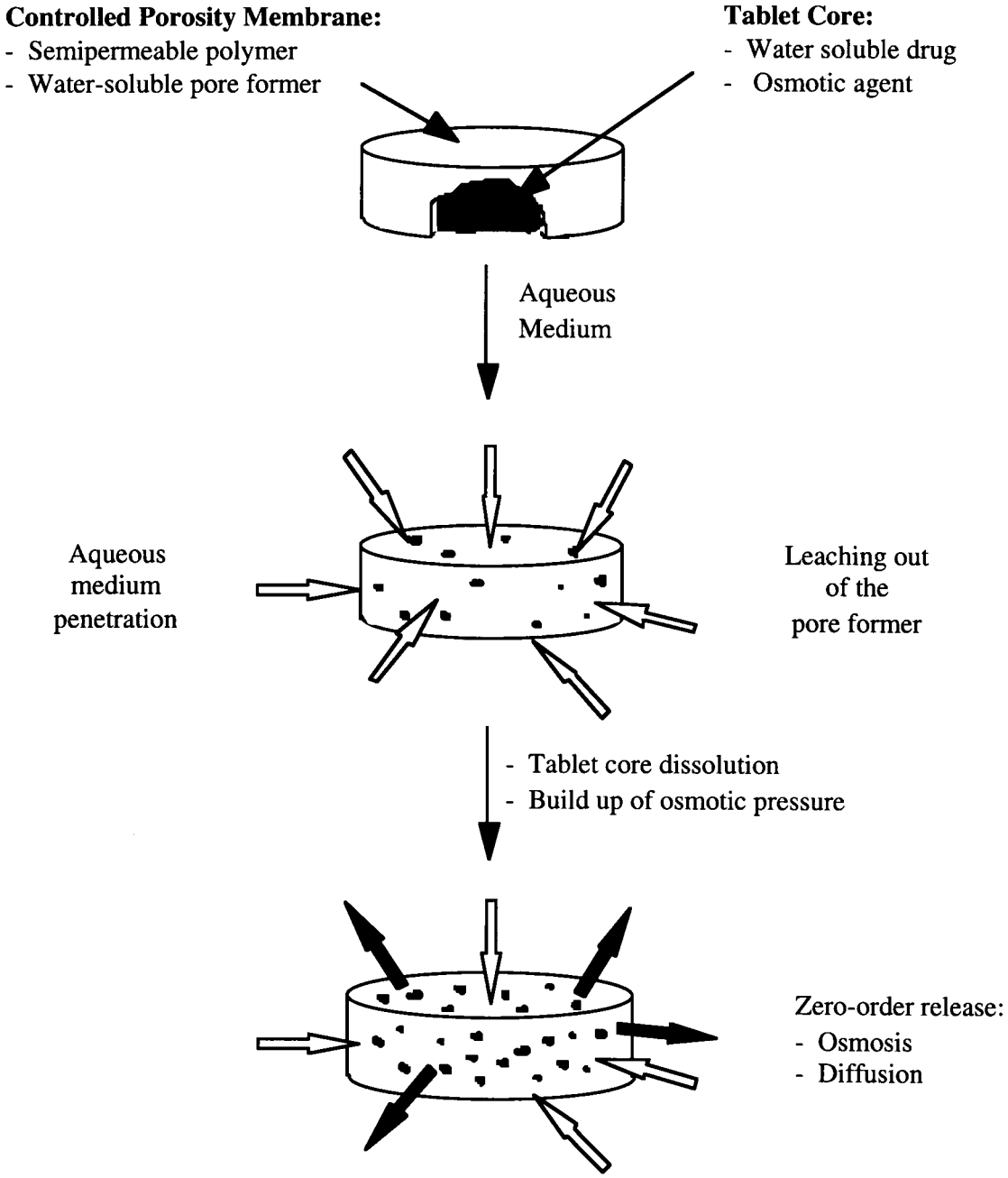


Scheme 1. Captisol® release rate (g/hr) from the controlled porosity osmotic pump tablet (115 μm membrane obtained from Formulation D (Ethylcellulose 4.5%, PEG 1450 4.0%, Ethanol/water 87.5/4.0%)) ($n = 3$).

coefficient of the drug between the aqueous medium and the membrane. This equation could only describe an apparent zero-order release pattern if all the parameters in the last two terms of this equation remain constant. Key factors are that the drug be present in excess of its solubility, S, and that $\Delta\Pi$, the osmotic pressure across the membrane remains relatively constant.

Until now, CP-OPT could not be applied to poorly water-soluble drugs. Tableting an osmotic agent and a poorly water-soluble drug results in water imbibing into the tablet but the poor solubility of the drug, in a largely unstirred environment, prevents the quantitative release of the drug over the desired period of 6–18 hours. This was shown in our earlier work [5–8] by tableting poorly water-soluble drugs in the presence of osmotic agents that had no solubilizing properties.

Captisol® or SBE_{7M}-β-CD, a sulfobutyl ether derivative of β-cyclodextrin (β-CD) variably substituted on the 2-, 3- and 6-position, hepta-sodium salt, with an average total degree of substitution (TDS) of seven, is not only an excellent solubilizer but also has strong osmotic properties. Two papers describing the osmotic properties of this and other CDs were recently published [9, 10]. Earlier papers described its *in vivo* safety and other desirable properties [11–14].

Okimoto et al., in a series of papers [5–8], performed a series of experiments in an effort to elucidate the relative contributions of osmotic *versus* diffusional release from both

a model system and actual tablets, see the first and second terms in Equation (1), respectively. It was concluded that the major contribution was primarily osmotic drug release with a contribution of up to 20 plus percent from diffusion.

Methods

Recently, using a novel die, Scheme 2, the release of a sparingly water-soluble drug, methylprednisolone, and Captisol® from some model tablets coated with various controlled porosity membranes was studied. Most of these studies involved a membrane consisting of ethylcellulose and the pore former polyethylene glycol 1450. This along with a series of measurements including the osmotic properties (using Differential Scanning Calorimetry and Vapor Pressure Osmometry) of Captisol®, its viscosity (Cone and Plate viscometer) and diffusion coefficient (pulsed field gradient ^{1}H-NMR) as a function of concentration. Independent measurements of drug and Captisol® permeability across isolated model membranes using a Side-by-Slide™ diffusion cell were also made. These measurements along with a determination of Captisol® concentration inside the tablet as a function of time allowed for a more complete picture of the temporal process. Complete details of all the procedures and experiments are available elsewhere [15].

Results and discussion

Figure 1 shows the near zero-order release rate of Captisol® from the model system shown in Scheme 2. Reasonable adherence to zero-order release is seen from 2–8 hours with a slight burst in the first two hours and a tailing of the release rate after eight hours. A key observation was the time dependency of Captisol® concentration inside the CP-OPT. This is shown in Table I. As expected, Captisol® concentration inside the tablet was changing with time and excess solid materials were only seen for the first 3–4 hours. That is, at the 1, 2, 3, 4 hour samples both solid and solution phases were seen inside the tablet. Post 4 hours only a solution phase was seen inside the tablet. Tables II and III show the dependency of Captisol® osmolality and osmotic pressure, and diffusion coefficient and viscosity (η) on concentration.

Clearly therefore, with all these changing parameters, Equation (1) should not be able to describe the near zero-order release rate seen in Figure 1. The data also suggest that the relative contributions from the osmotic effect and the diffusional terms may be changing with time. An additional factor not directly accounted for in Equation1 is the influence of viscosity on the hydrostatic pressure inside the tablet. The volumetric flow rate (dV_t/dt) due to osmotic pumping, of a solute solution across a semipermeable membrane can be described by Equation (2) [15]:

$$\frac{dV_t}{dt} = \frac{A}{h} L_p(\sigma \Delta\Pi - \Delta P), \qquad (2)$$

Table 1. Captisol® concentration inside the controlled porosity osmotic pump tablet (115 μm membrane (Ethylcellulose 4.5%, PEG 1450 4.0%, Ethanol/water 87.5/4.0%)) ($n = 2$)

Time (hours)	Captisol® concentration (mol/L)
1*	0.36
2*	0.34
3*	0.33
4*	0.28
6	0.24
8	0.23
10	0.20
12	0.18

*At the 1, 2, 3, 4 hour samples both solid and solution phases were seen inside the tablet. Post 4 hours only a solution phase was seen inside the tablet.

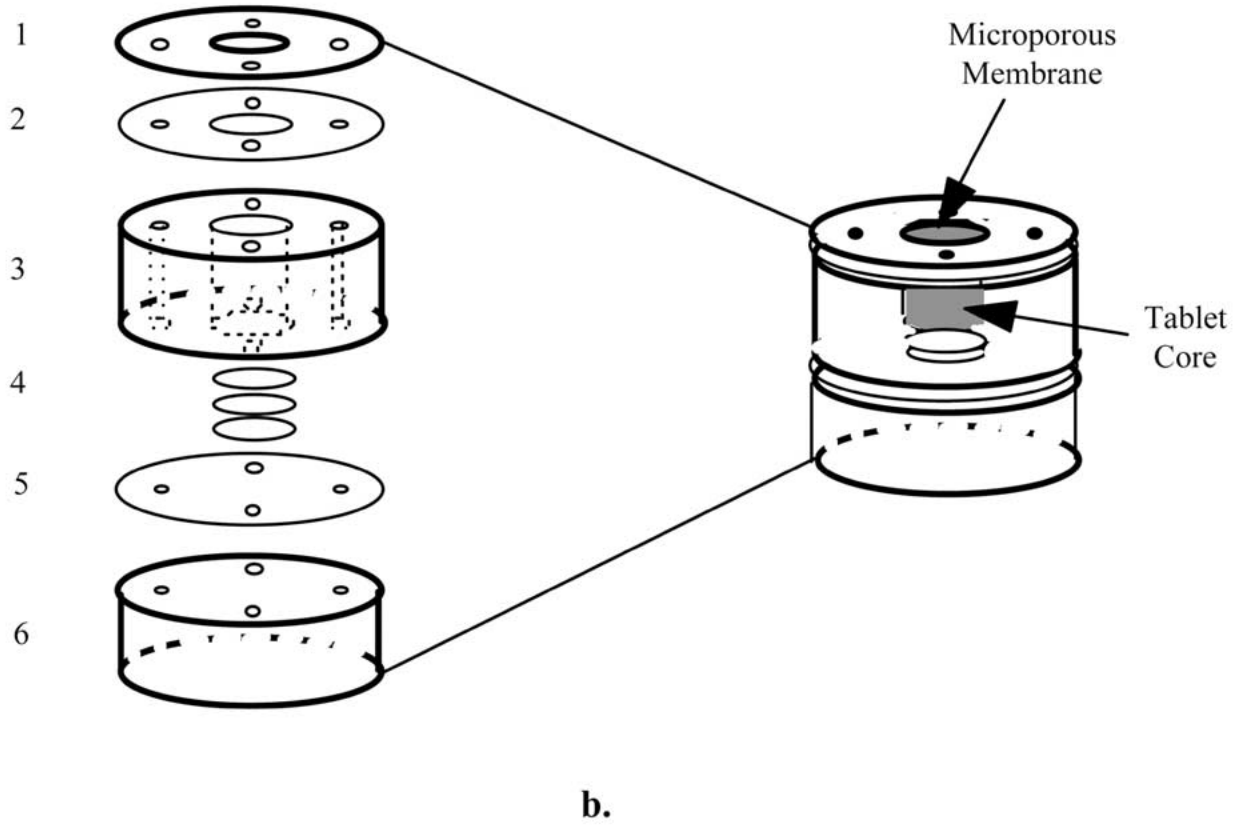
Table 2. Captisol® osmotic pressure measured by vapor pressure osmometry

Captisol®			
Concentration		Osmolality (Osm/kg)	Osmotic pressure (atm, 37 °C)
mol/kg	mol/L	Avg±Std	Avg±Std
0.005	0.005	0.030± 0.001	0.8± 0.0
0.010	0.010	0.060± 0.004	1.5± 0.5
0.060	0.050	0.297± 0.004	7.5± 0.1
0.120	0.100	0.749± 0.014	19.1± 0.4
0.200	0.160	1.367± 0.009	34.8± 0.2
0.280	0.210	1.960± 0.002	49.9± 0.1
0.390	0.260	3.028± 0.002	77.1± 0.0
0.530	0.310	4.140± 0.007	105.4± 0.2
0.700	0.360	6.549± 0.009	166.7± 0.2

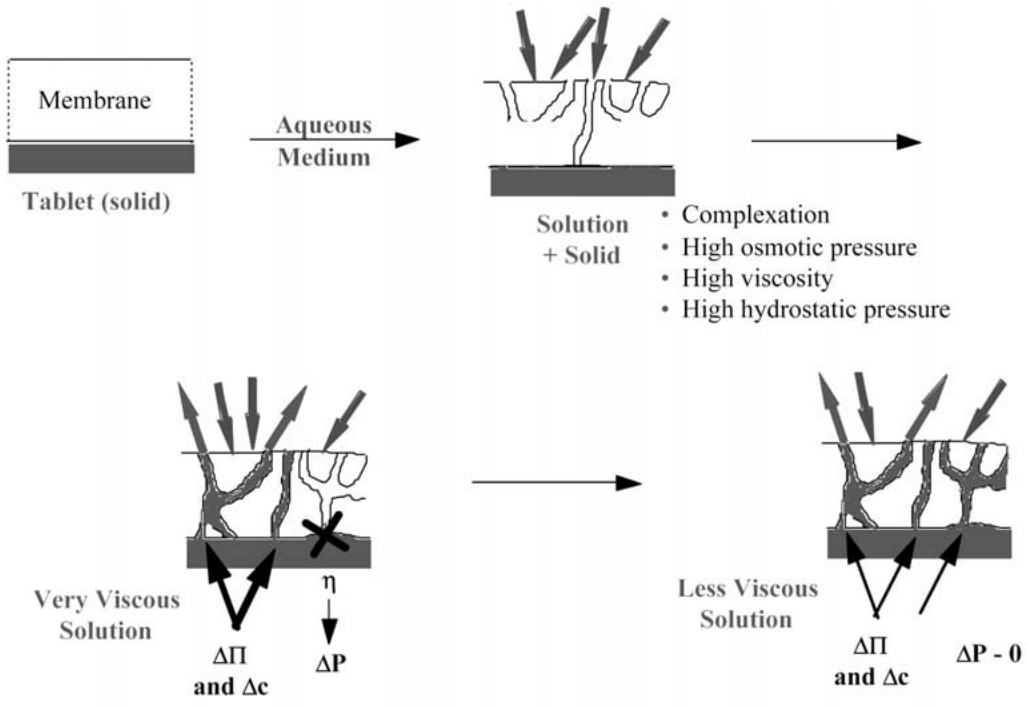
Table 3. Captisol® diffusion coefficient (D_{D2O}) and viscosity (η) in D_2O at 37 °C

Concentration (mol/L)	$D_{D2O} \pm$ std ($\times 10^{-6}$ cm^2/sec)	$\eta \pm$ std (cP) ($n = 3$)
0.01	4.099 ± 0.030	0.74 ± 0.00
0.01	3.020 ± 0.052	1.01 ± 0.00
0.10	2.025 ± 0.036	1.71 ± 0.02
0.15	1.135 ± 0.036	3.38 ± 0.17*
0.25	0.418 ± 0.017	16.53 ± 0.58*

* indicates viscosity measured in water using the Cone and Plate viscometer.



Scheme 2. CP-OPT simulator: (a) elements, (b) assembled. 1. Hollow stainless steel cover, 2. Hollow Teflon^{TM} sheet, 3. Hollow stainless steel die, 4. Teflon^{TM} inserts, 5. Teflon^{TM} sheet, 6. Stainless steel platform.



Scheme 3.

where A, h, L_p and σ are the surface area, thickness, hydraulic conductivity and reflection coefficient of the membrane, respectively, and $\Delta\Pi$ and ΔP are the difference in osmotic pressure and in hydrostatic pressure across the membrane, respectively. Theeuwes [4] and others [1, 16] have applied this equation to OPTs by assuming that ΔP was negligible. In the CD-based CP-OPT, however, ΔP is not believed to be negligible and is expected to decrease the volumetric flow rate by increasing resistance to flow. Therefore, a general expression was developed from basic principles to describe the volumetric flow rate of solute due to osmotic pumping ($\Delta\Pi$) when the difference in hydrostatic pressure across the membrane (ΔP) is not negligible. Using Poiseuille's law, which relates hydrostatic pressure to viscosity, it is possible to modify Equation (1) to include the resistance to volumetric flow through the micropores of the membrane as indicated by the term ΔP in Equation (2). Neglecting the diffusional contribution to Equation (1), this results in Equation (3).

$$\frac{\mathrm{d}M_t}{\mathrm{d}t} = \frac{\mathrm{d}V_t}{\mathrm{d}t}c_t = \frac{AL_p\sigma\Delta\Pi}{h + AL_pk\eta}c_t. \qquad (3)$$

Since the relationship between Captisol® and viscosity, η, can be determined from the data shown in Table III it will be possible to project the contribution from the osmotic driving force as a function of time. That analysis will be the basis for a future publication. Qualitatively, the sequence of events is illustrated in Scheme 3. The apparent zero-order release mechanism may be related to countering physical properties as the concentration of Captisol® changes within the tablet core. The initial concentration of Captisol® within a core is 0.3–0.4M, see Table I. As Captisol® is released, osmotic pressure drops across the membrane but so does viscosity. As the viscosity within the tablet drops, the apparent diffusion coefficient of both Captisol® and drug/ Captisol® complex increases. Therefore, it appears that there is hydraulic pressure resistance to fluid flow from the tablet through the micropores of the membrane. This resistance decreases with time due to the drop in viscosity so that even as osmotic pressure ($\Delta\Pi$) and concentration differences (Δc) drop with time, counter balancing faster release occurs. Osmotic driving force appears to be the most important initial driving force but a diffusional component becomes more significant with time.

Acknowledgements

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