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Brief/Technical Note

Carvedilol: Solubilization and Cyclodextrin Complexation: A Technical Note

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INTRODUCTION

Carvedilol (Table I) is a non-selective β-blocker indicated in the treatment of mild to moderate congestive heart failure. It also has vasodilating properties that are mainly attributed to its α_1-blocking activity, as well as ability to inhibit oxidative stress in coronary smooth muscle (1). It is marketed under various trade names including Eucardic (Roche), Dilatrend (Roche), Kredex (Roche) and Coreg (GlaxoSmithKline). Carvedilol is well absorbed after oral administration, but is subject to first-pass metabolism in the liver resulting in only about 25% absolute bioavailability. Common oral dosage is 25 mg/day (dose/solubility ratio ≥250 ml; class II drug according to the BCS) with peak plasma concentrations occurring 1 to 2 h after the administration and elimination half-life of 6 to 10 h (2). Low aqueous solubility ($S_0 \approx 0.02$ mg/ml at pH 7.4) hampers formulation of carvedilol as, for example, nasal spray or sublingual tablet. It has been shown that carvedilol forms 1:2 drug/cyclodextrin complexes with the natural β-cyclodextrin (βCD; 3). 2-Hydroxypropyl-βCD (HPβCD) and sulfobutylether βCD (SBEβCD) have been used as complexing agent in carvedilol buccal and sustained release tablets (4–6).

Cyclodextrins (CDs) are cyclic oligosaccharides that in recent years have been introduced to the pharmaceutical industry as novel enabling excipients, mainly as solubilizing complexing agents for enhanced drug bioavailability (7,8). CDs consist of six (αCD), seven (βCD), eight (γCD) or more α-1,4-linked α-D-glucopyranose units forming a somewhat truncated cone. The hydroxy groups are oriented towards the cone exterior making the external surface hydrophilic while the central cavity is lined by the carbons and ethereal oxygens of the carbohydrate skeleton making it somewhat hydrophobic. CDs form inclusion complexes by taking up lipophilic drug molecule, or more frequently some lipophilic moiety on the drug molecule, into the lipophilic central cavity. Although such inclusion complexes are the most common form of drug/CD complexes the hydroxy groups on the outer surface of the CD molecule are able to form hydrogen bonds with other molecules and CDs can, like non-cyclic oligosaccharides and polysaccharides, form water-soluble non-inclusion complexes with lipophilic water-insoluble drugs (9–11). In saturated aqueous solutions drug/CD complexes frequently consist of a mixture of inclusion and non-inclusion complexes (12). CDs and CD complexes are also known to self-associate to form nanoscale aggregates (12–14) and these aggregates are thought to be able to solubilize lipophilic drug molecules in micellar-like fashion (15).

Although CDs are effective solubilizer of drugs their solubilizing efficiency can sometimes be inadequate due to low intrinsic solubility of the drug or low stability constant of the drug/CD complex (16,17). Various methods have successfully been applied to enhance the solubilizing effects of CDs including drug ionization, formation of somewhat water-soluble drug salts and ternary complex formation (8,15, 18,19). Salt formation is the most common method of increasing the apparent intrinsic solubility of acidic and basic drugs and frequently enhanced drug solubilization can be obtained by combining salt formation and cyclodextrin complexation. The purpose of this present study is to investigate the effects of ionization and salt formation on CD solubilization of carvedilol.

MATERIALS AND METHODS

Materials

Carvedilol was kindly supplied by GlaxoSmithKline (King of Prussia, PA, USA). α-Cyclodextrin, MW 972 Da (αCD), β-cyclodextrin, MW 1,135 Da (βCD), γ-cyclodextrin, MW 1,297 Da (γCD) and 2-hydroxypropyl-γ-cyclodextrin with molar substitution of 0.6, MW 1,576 Da (HPγCD) from Wacker Chemie (Burghausen, Germany), 2-hydroxypropyl-β-cyclodextrin with molar substitution of 0.6, MW 1,400 Da (HPβCD) from Roquette (Lestrem, France), and sulfobutylether β-cyclodextrin sodium salt with molar substitution of 0.9, MW 2,163 Da (SBEβCD) was kindly donated by CyDex Inc. (Kansas City, KS, USA). Hydroxypropyl methylcellulose (HPMC) was obtained from Mecobenzon (Denmark). All other chemicals used were of analytical reagent grade purity.

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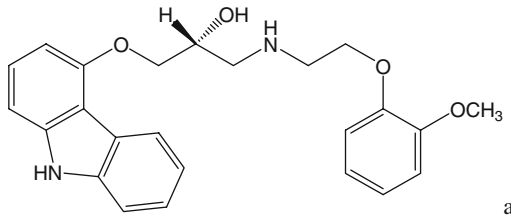
Table I. Carvedilol ((2*RS*)-1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol): structure and physicochemical properties



and enantiomer

Molecular weight: 406.5 Da
Melting point: 114-115°C (at least two polymorphic forms)
pKa: 7.8
Log *P* (octanol/water) at initial carvedilol conc. of 6×10^{-7} M and room temp.:
pH 9.0: 3.10
pH 7.0: 2.74
pH 5.0 1.93
pH of an aqueous 10% (w/v) suspension at room temp.: 7.6-7.7
Solubility in pure water at 25°C (mg/mL):
Free base: 0.01
Hydrochloride: 1
Adipate: 0.3
Tartrate: 0.7
Methanesulfonate: 10
Solubility of the free base in aqueous buffer solutions at 25°C (mg/mL):
pH > 9.0: < 0.001
pH 7.4: 0.02
pH < 5: 0.10

Based on the following references: European Pharmacopoeia 5.06, pp. 1193–1194 and (23,29–32).

Solubility Studies

The solubility of carvedilol in water or aqueous CD solutions was determined by a heating method (17). First, the stability of carvedilol in the aqueous complexation media was evaluated. Small amount (1 mg/ml) of the drug was dissolved in the aqueous complexation media containing 5% (*w*/*v*) of SBEβCD, RMβCD or HPβCD. The solution was then divided into six sealed vials that were heated in an autoclave for from zero to five heating cycles; each cycle consisted of heating to 121 °C for 20 min and cooling to room temperature. The carvedilol concentration in the vials was then determined by a high-performance liquid chromatographic method (HPLC). The vials were protected from light during the testing procedure. About 3% carvedilol degradation was observed during five heating cycles in an autoclave but less than 1% degradation was observed during one heating cycle. The drug solubility was then determined as follows. Specific amount of a given CD was dissolved in water or aqueous complexation medium containing water-soluble polymer or buffer salts. In some experiments water was replaced by aqueous acetic acid, phosphoric acid or hydrochloric acid solution, or aqueous 0.1 M acetate buffer (pH 4.7) or aqueous 0.1 M disodium hydrogen phosphate (Na_2HPO_4) buffer solution (pH 6.8). In some cases 0.25% (*w*/*v*) HPMC was present in the aqueous complexation medium. An excess amount of carvedilol, the free base, was added to the medium and the suspension formed was placed in a sealed container and heated in an autoclave (121 °C for 20 min). After cooling to ambient temperature the container was opened and a small amount of solid carvedilol added to the container to promote drug precipitation. After equilibration at ambient temperature (22–23 °C) in a sealed container under constant agitation for at least 4 days, the suspension was filtered through a 0.45 μm membrane filter (discarding approximately the first third of the filtrate) and the solution analyzed by HPLC (after dilution with 70% aqueous methanol solution, if necessary). The time needed to reach equilibrium solubility was determined by analyzing samples of the equilibrating solution at different time points to establish constant drug solubility.

The complexation efficiency (CE) was determined from the linear phase-solubility diagram (a plot of the total drug solubility ($[carvedilol]_t$) *versus* total cyclodextrin concentration ($[CD]_t$) in moles per liter):

$$CE = \frac{Slope}{1 - Slope} = \frac{[carvedilol/CD]}{[CD]} = K_{1:1} \cdot S_0 \qquad (1)$$

where [carvedilol/CD] is the concentration of dissolved complex, [CD] the concentration of dissolved free cyclodex-

trin, Slope is the slope of the linear phase-solubility profile (in the range 0 to 20% *w/v* CD), $K_{1:1}$ is the apparent stability constant of the carvedilol/CD complex, assuming 1:1 stoichiometry based on the linearity of the profile, and S_0 is the intrinsic solubility of carvedilol in the aqueous complexation medium (17,20).

Permeation Studies

Drug flow through two different types of semi-permeable cellophane membranes with molecular weight cutoff (MWCO) of 3,500 Da and 6,000–8,000 Da (Spectra/Pore membranes from Spectrum Laboratories Inc., Rancho Dominguez, USA) was measured in Franz-diffusion cells (FDC400 15 FF) from Vangard International Inc. (Neptune, USA) where the donor phase (2 ml) is unstirred but the receptor phase (12 ml) is stirred with a magnetic stirrer during the experiment. The area (A) of the exposed membrane was 1.77 cm^2. The donor phases consisted of water, or 3% (*v/v*) acetic acid solution in water, containing 0, 5, 10 or 20% (*w/v*) HPβCD solution saturated with carvedilol where the pH of the acetic acid free solutions was adjusted to 3.7 with concentrated phosphoric acid. The mean pH (±SD) of all the donor phases was 3.66± 0.45. The receptor phase contained the same concentration of HPβCD as in the donor phase. In all cases a linear increase in the amount of drug in the receptor phase (q) with time (t) was observed indicating that the barrier function of the membrane was constant during course of the experiment. The membrane was allowed to equilibrate with the aqueous receptor phase over night. The flux through the membrane was determined at room temperature (22–23 °C). Samples were withdrawn from the receptor phase at various time points up to 6 h and the flux (J) was calculated from the linear slope (dq/dt) of each permeability profile and the carvedilol concentration in the receptor phase (Eq. 2) determined by HPLC.21 The concentration (solubility) of carvedilol in the donor phase (C_d) was determined by HPLC. The results presented are the means and the standard deviation (SD) of four separate experiments.

$$J = \frac{dq}{A \cdot dt} = P \cdot C_d \qquad (2)$$

Quantitative determinations

The quantitative determination of drugs were performed on HPLC equipment consisting of Agilent 1100 Series, adjusted to 242 nm, with autoinjector, ChemStation Rev. A.0901 and Luna C18 (150×4.6 mm) 5 μm column. The mobile phase consisted of methanol and aqueous 0.2% (*v/v*) phosphoric acid solution (1:1), the flow rate was 1.0 ml/min and the retention time was 5.1 min.

RESULTS AND DISCUSSION

Carvedilol is a lipophilic and somewhat water-insoluble drug that forms water-soluble salts at low pH (Table I). During the solubility studies it was observed that the carvedilol solubility did decrease when the pH of the aqueous acetate solutions was adjusted with concentrated hydrochloride solutions. Addition of phosphoric acid had less effect on the solubility than hydrochloric acid. It is known that different pH-adjusting acids can have significant effect on the aqueous solubility of weak base and that the solubility product of the protonated base and the anionic form of the acid can result in significant solubility deviations (22–24). This could explain why we were observing lower solubility when the pH was adjusted with hydrochloric acid. In fact, solubility studies in dilute aqueous hydrochloric acid (0.2 M), phosphoric acid (0.1 and 0.3 M) or acetic acid (0.2 to 0.5 M) solutions, where the pH was monitored but not adjusted (i.e. no additional buffer salts were added to the medium), showed that the hydrochloride was 10 times less soluble than the phosphate and over 400 times less soluble than the acetate (Fig. 1). In hydrochloric acid and phosphoric acid maximum solubility was observed at pH between 1 and 2. Excess amounts of the acids (pH below 1.5) resulted in some lowering of the solubility due to the solubility product effect (or common-ion effect;22,24). Based on this observation pH-adjustments with hydrochloric acid, and addition of excipients containing chloride ions, was avoided. In general, only acetic acid was used for pH-adjustments but phosphoric acid was used if pH-adjustment was needed at constant acetic acid concentrations and for preparation of aqueous reference solutions containing no acetate (in the phase-solubility and permeation studies).

The complexation efficiencies (CE) of various CDs are shown in Table II. The CE was determined from the linear phase-solubility diagrams of carvedilol in the various cyclodextrin solutions, in pure water or aqueous buffer solutions, according to Eq. 1. The intrinsic solubility (S_0) is the determined solubility in the aqueous complexation medium when no CD is present, i.e. S_0 is not necessarily equal to the y-intercept of the phase-solubility diagram. The βCDs had the highest CE followed by the γCDs, which had somewhat lower CE, and αCD which had much lower CE than all other CDs tested. In aqueous 1% (*v/v*; 0.17 M) acetic acid solution

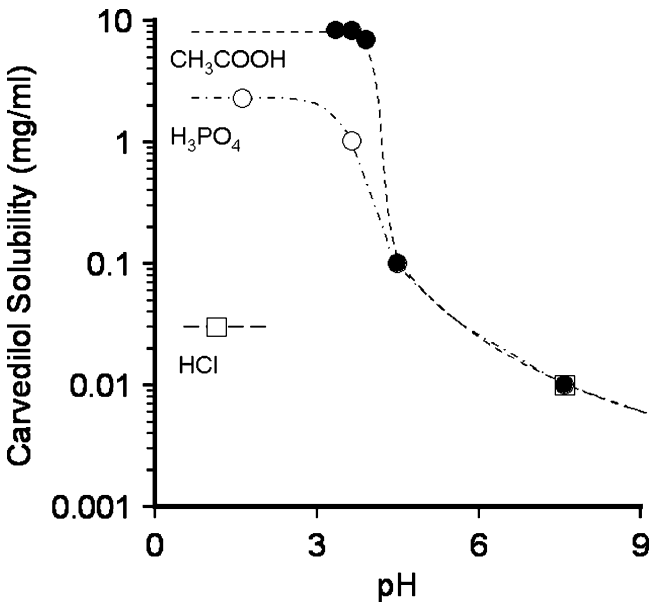


Fig. 1. The effect of different pH-adjusting acids on the aqueous solubility of carvedilol at room temperature (22–23 °C); (*filled circle*) acetic acid, (*open circle*) phosphoric acid and (*open square*) hydrochloric acid

Table II. The Complexation Efficiency (CE) and the Drug/CD Molar Ratio in Aqueous CD Solutions Saturated with the Drug

Cyclodextrin (conc. range)[a]	pH[b]	*S* (mg/ml)[c]	Additive (conc.)[d]	CE[e]	Molar Ratio[f]
αCD (0.0–2.0% *w/v*)	W	0.01	–	0.02	1:40
βCD (0.0–2.0% *w/v*)[g]	W	0.01	–	0.23	1:5
βCD (0.0–2.5% *w/v*)[g]	W (3.8)	7	Acetic acid (1.0% *v/v*)	0.65	1:3
HPβCD (0.0–20% *w/v*)	W (3.7)	1	Phosphoric acid	0.05	1:23
HPβCD (0.0–20% *w/v*)	W (3.7)	7	Acetic acid (1.0% *v/v*)	1.62	1:1.6
SBEβCD (0.0–17% *w/v*)	W (3.8)	7	Acetic acid (1.0% v/v)	1.10	1:2
SBEβCD (0.0–17% *w/v*)	4.7	0.1	0.1 M Acetate buffer	1.60	1:2
SBEβCD (0.0–17% *w/v*)	4.7	0.1	0.1 M Acetate buffer, HPMC (0.25% *w/v*)	1.60	1:2
SBEβCD (0.0–17% *w/v*)	6.8	0.02	0.10 M Na_2HPO_4	0.33	1:4
SBEβCD (0.0–17% *w/v*)	6.8	0.02	0.10 M $Na2HPO_4$, HPMC (0.25% *w/v*)	0.86	1:2
γCD (0.0–2.0% *w/v*)	W	0.01	–	0.36	1:4
HPγCD (0.0–13% *w/v*)	6.8	0.02	0.10 M Na_2HPO_4	0.25	1:5
HPγCD (0.0–13% *w/v*)	6.8	0.02	0.10 M Na_2HPO_4, HPMC (0.25% *w/v*)	0.09	1:11

[a] Cyclodextrin concentration range of the linear phase-solubility profile
[b] pH of the complexation medium; W = unbuffered aqueous solutions
[c] Approximate solubility in the complexation medium when no cyclodextrin is present (22–23 °C)
[d] Additives and their concentration in the complexation medium; *HPMC* hydroxypropyl methylcellulose
[e] Complexation efficiency according to Eq. 1
[f] Drug:cyclodextrin molar ratio in the lyophilized complex = 1: (CE+1)/CE
[g] The aqueous solubility of βCD in pure water has been determined to be 1.85% (*w/v*). However, in aqueous acetic acid solution containing carvedilol it is somewhat higher (26)

(pH 3.8) the natural cyclodextrins gave B_S-type phase-solubility profiles (25) with maximum carvedilol solubility of about 15 mg/ml at 5% (*w/v*) αCD, about 25 mg/ml at 10% (*w/v*) βCD and about 23 mg/ml at 15% (*w/v*) γCD. Although the solubility of the natural βCD in pure water is only 1.85% (*w/v*) the total solubility of βCD, i.e. βCD and the βCD complex, is frequently much greater or as here 10% (26). The solubility of carvedilol in aqueous 1% (*v/v*) acetic acid solution was determined to be 6.91±0.20 mg/ml (mean±SD of three separate determinations). At pH 3.8 carvedilol (p*K*a 7.8) is in its protonated form and forms a water-soluble acetate salt. Carvedilol phosphate and hydrochloride had much lower solubility. Enhanced solubility, especially when the acetate was formed, frequently resulted in increased CE. Much less carvedilol solubilization was observed in pure water or at higher pH, where the drug is only partly ionized, corresponding to lower CE (Table II). Since free drug in solution is in equilibrium with the drug/CD complex increasing drug solubility through salt formation will push the equilibrium towards the complex formation. Thus, although the stability constant of the drug/CD complex usually decreases with increased ionization (i.e. increased polarity) of the drug the CE, which is the product of the solubility (*S*) and the stability constant ($K_{1:1}$), frequently increases (see Eq. 1). Adding HPMC to the complexation medium enhanced the CE of SBEβCD at neutral pH. Although SBEβCD had the highest affinity for the carvedilol cation, due to the attraction of the cationic drug and the anionic SBEβCD, the overall highest CE was obtained with HPβCD in aqueous 1% (*v/v*) acetic acid solution and, thus HPβCD was selected for further studies (Table II).

The phase-solubility profile of carvedilol in aqueous HPβCD solutions, containing either 3% *v/v* (0.5 M) acetic acid (pH 3.7) or sufficient phosphoric acid to adjust the pH to 3.7, is shown in Fig. 2. Both profiles are of A_L-type indicating that the complex is first-order with respect to CD and first or higher order with respect to the drug (20). Identical isotherms were obtained when the concentrations of the dissolved drug and CD were expressed in moles/liter resulting in slopes of 0.043 (phosphoric acid) and 0.6181 (acetic acid). These slope values were then used to calculate the CE according to Eq. 1. Corresponding intrinsic solubilities, i.e. solubility of the drug in the aqueous complexation media when no CD was present, were determined to be 0.0025 M and 0.0202 M, respectively. The higher aqueous solubility of carvedilol acetate results in higher CE. Although a slope of less than one does not exclude the occurrence of higher order complexes, an 1:1

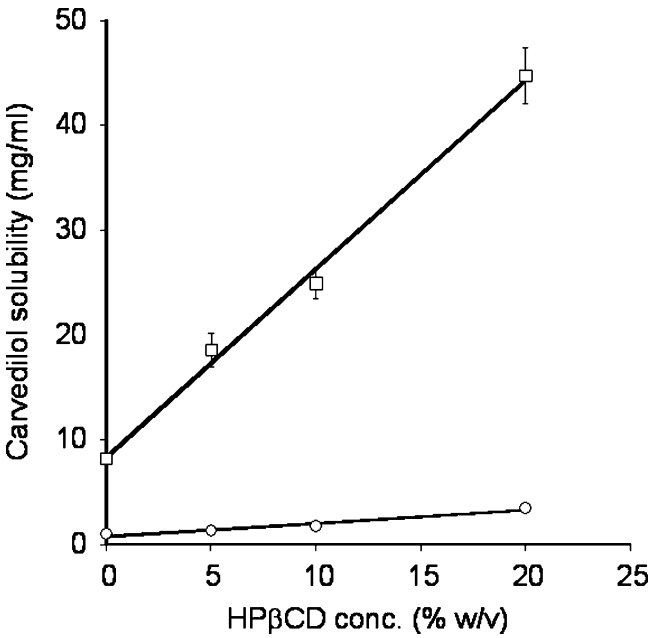


Fig. 2. Phase-solubility profiles of carvedilol in pure aqueous HPβCD solution (*open circle*) and in aqueous HPβCD solution containing 3% *v/v* acetic acid (*open square*)

drug/CD complex is often assumed in the absence of other information. Carvedilol/CD complexation ratio of 1:2 should result in A_P-type phase-solubility diagrams which were not observe under current experimental conditions.

At acidic pH carvedilol is a lipophilic cation that can possess amphiphilic properties and has consequently the potential of forming micellar-type structures at low pH. However, the aggregation number (N) of amphiphilic drugs is usually much lower ($N \approx 4$ to 20) than those of micelles formed by alkyl chain detergents ($N \approx 50$ to 200) (27). Furthermore both CDs and drug/CD complexes are known to form aggregates and it is known that acetate ions are able to interact with drug/βCD complexes enhancing their apparent solubility in aqueous solutions, for example the aqueous solubility of hydrocortisone in βCD solutions increases when acetate is present in the aqueous complexation medium (12–15). This has been related to the ability of acetate ions to form non-inclusion complexes with drug/CD complexes and drug/CD complex aggregates. Such aggregates have been detected in aqueous solutions by transmission electron microscopy (13). Studies have shown that the mean hydrodynamic radius of CD aggregates increases with increasing CD concentration and, thus, it is possible to estimate the increase in aggregate size by determining the drug flux through semi-permeable membranes of different molecular weight cutoff (MWCO) (12,13,21,28). Flux studies were applied to detect self-association or CD aggregate formation (Fig. 3). Aqueous solutions containing from 0 to 20% (*w*/*v*) HPβCD in either phosphoric acid or 3% (*v*/*v*) acetic acid were saturated with carvedilol. The pH of the solutions was 3.66±0.45. The carvedilol flux (J) from the HPβCD solutions was determined through two different semi-permeable cellophane membranes with MWCO 3,500 and 6,000–8,000. The molecular weight (MW) of a 1:1 carvedilol/HPβCD complex is 1,807 Da and thus both the free drug (MW 406.5 Da) and the complex should be able to permeate the membranes and in that case there should be a linear relationship between the total amount of dissolved drug (C_d) and J in Eq. 2 (see Figs. 2 and 3). However, the J *versus* HPβCD concentration profiles through the MWCO 3,500 Da membrane show slight decrease in J with increasing HPβCD concentration from the phosphoric acid solution but a slight increase at 5 and 10% HPβCD from the acetic acid solutions (Fig. 3). In the case of the MWCO 6,000–8,000 Da membrane about 25% initial increase in J was observed with increasing HPβCD concentration before J levels off for both the phosphate and the acetate solutions. This indicates that in the beginning relatively small drug/CD aggregates are formed that are able to permeate the membranes, but at higher HPβCD concentrations the aggregates become too large to permeate the MWCO 6,000–8,000 Da semi-permeable membrane. Furthermore, the increase in the carvedilol solubility with increasing HPβCD concentration from 0 to 20% (*w*/*v*) was 3.4-fold for the phosphate solution and 5.4-fold for the acetate solution (Fig. 2). In Fig. 3 the J ratio between the phosphate and the acetate solutions (mean ratio±SD: 6.5±0.7) was approximately the same as between carvedilol solubility in the two solutions when no CD was present (solubility ratio 8.1). Again this indicates that mainly the free carvedilol or the carvedilol acetate salt permeates the membranes. The carvedilol/HPβCD complex is only responsible for up to 25% of the carvedilol flux through the MWCO 6,000–8,000 Da membrane and only up to 15% through the MWCO 3,500 Da membrane. The carvedilol flux ratio between the two membranes ranged from 1.0 for phosphate solution containing no CD to 1.5 for the acetate solution containing 20% HPβCD. In summary, the flux studies indicate that the carvedilol/HPβCD forms aggregates of two or more carvedilol/HPβCD complexes at relatively low HPβCD concentrations.

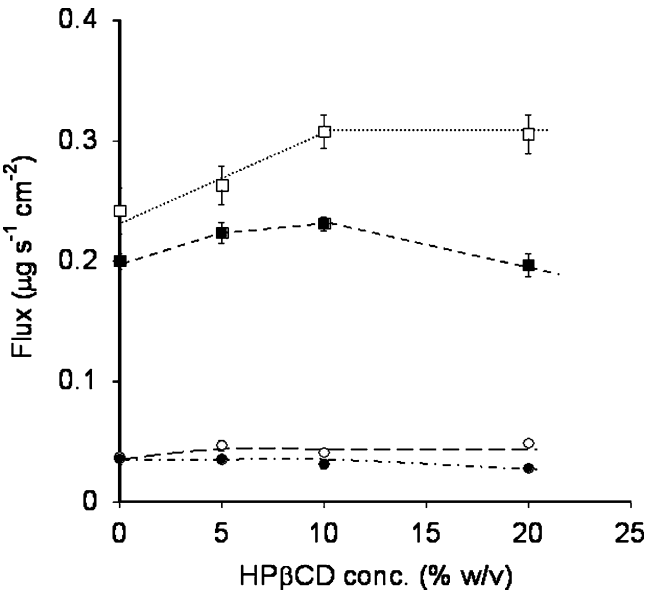


Fig. 3. Flux–HPβCD concentration profiles through semi-permeable cellophane membranes (*filled square* and *filled circle*: MWCO 3500; *open square* and *open circle*: MWCO 6,000–8,000), from aqueous 3% (*v*/*v*) acetic acid solution (*open square* and *filled square*) and aqueous phosphate solution (*open circle* and *filled circle*)

Although the ionized carvedilol can possibly self-associate the N value, i.e. the number of carvedilol molecules per aggregate species, must be less than five to seven (MW of the carvedilol acetate aggregates from 2,335 to 3,269 Da) since higher N values would result in marked decrease in the carvedilol flux, especially through the MWCO 3,500 Da membrane. It is also worth noting the flux of carvedilol from CD-free solutions through the 3,500 membrane (J=0.0359±0.0045 mg s^{-1} cm^{-2}) is identical to the one through the 6000–8000 membrane (J=0.0376±0.0012 mg s^{-1} cm^{-2}) when no acetate is present but 0.2003±0.0065 mg s^{-1} cm^{-2} and 0.2422±0.0188 mg s^{-1} cm^{-2}, respectively, when acetate is present (Fig. 3). The larger flux through the 6000–8,000 membrane could indicate that aggregates of carvedilol acetate are being formed that are unable to permeate through the 3500 membrane.

SUMMARY AND CONCLUSIONS

At pH below 5 addition of acetic acid results in significant increase in the aqueous solubility of carvedilol. This increase is due to formation of carvedilol acetate salt that has significant higher solubility than the hydrochloride or phosphate. The apparent increase in S_0 (due to the acetate formation) increases CE of uncharged CDs such as HPβCD,

decreasing the amount of CD needed to solubilize given amount of drug. Flux studies indicate that the carvedilol/HPβCD complexes form water-soluble aggregates in aqueous solutions.

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