Effect of water-soluble polymers and cosolvent on with candisartan–cyclodextrin complex solubility

MUDER AL HAYDER[1], ZAID AL OBIADY[2], HASSANAIN SHAKER MAHMOOD[3], HUSAM H. TIZKAM[4]

Department of pharmaceutics, College of Pharmacy, University of Kerbala, Iraq

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ABSTRACT

Objective: The aim of the study is to find the candesartan celexitile (CC) solubility profile in the presence of ß-cyclodexrin, poloxamer 188 and PEG 400 and the synergism effect of the cosolvency of PEG 400 and the solubilizing effect of polymer poloxamer 188 on the drug cyclodextrin complex.

Methods: An excess amount of (CC) was added to 10 mL aqueous solutions containing range concentrations of either poloxamer 188 (0−0.4% w/v), β-CD (0−1%, w/v) or PEG (0−50%,v/v) at 25±1 ºC separately. The mixtures of aqueous solution were shaken in a thermostated water bath at 25°C ± 2 for 24 h to reach equilibrium. After that, all the suspensions were filtered through 0.22 µm syringe filter and assayed for (CC) by UV Spectrophotometer at ʎ of 255 nm. Phase solubility diagrams were plotted with (CC) solubility versus either ß-CD, poloxamer or PEG 400 concentration separately.

Results: It was found that the solubility of (CC) increased with the increasing concentration of poloxamer188, PEG 400 or ß-CD. The phase solubility curves of (CC) in aqueous solution at 25°C of ß-CD was of Higuchi's AL-type confirming the formation of 1:1 complexes. The synergism effect of poloxamer 188 and PEG 400 on the solubility of (CC) in the presence ß-CD was marked. The values of stability constants (K*sp*) of drug- ß-CD complexes and in the presence of PEG 400 or poloxamer 188 with 0.4 mg / ml ß-CD were 59.7, 5.8 and 195.8 M^{-1} respectively. Addition of poloxamer 188 to the drug-ß-CD complex increase the constant stability while addition of PEG 400 decrease the constant stability of the complex.

Conclusion: The solubility profile of (CC) in the presence of CD followed Higuchi equation confirming the formation of 1:1complexes of AL-type. The synergism effect of the polymer on the CC-CD complexes was significant.

ملخص البحث

تأثير البوليمر او مساعد المذيب على ذوبانية كاندسارتان سلكستيل معقد مع بتا سايكلودكسترين.

تهدف هذه الدراسة لمعرفة ذوبانية الكانديسارتان سليكستيل في المحاليل المائية مع البيتا سيكلودكترين و البولوكزامر 188 والبولي اثيلين كلايكول 400 كما تهدف الدراسة لمعرفة التاثير التازري لمساعد المذيب البولي اثلين كلاكول او التاثير الاذابي للبوليمر بولوكزامر 188 لاذابة الكانديسارتان بوجود السايكلودكسترين.

أضيفت كمية كثيرة من الدواء مع تراكيز مختلفة من البولوكزامر (0-4%) و من البتا سايكلودكسترين (0-1%) و من البولي اثلين كلايكول (0-50%) في 10 ملم من الماء المقطر وقد بقي في الهزاز لمدة 24 ساعة وفي درجة حرارة25±1 ^{o}C حتى يصل الى مرحلة التوازن. المزيج الناتج قد فلتر وفحص من خلال UV Spectrophotometer at λmax of 255 nm . الرسوم البيانية لطريقة الذوبان قد رسمت من خلال العلاقة بين معدل الذوبان مع التراكيز المختلف للمساعدات الاذابة.

النتائج التي وجدت ان الدواء يزداد ذوبانا كلما زاد تركيز المواد المساعدة على الاذابة وأن نوع الترابط بين السايكلودكسترين مع الدواء كانت خاضعة الى معادلة Higuchi's التي تمثل نوع AL-type الذي يؤكد نوع المركب المعقد مكون من 1:1 بين الدواء والسايكلودكسترين. معدل الثباتية لانواع المحاليل التي تحتوي على تراكيز مختلفة من السايكلودكسترين لوحده او بوجود تراكيز مختلفة من البولي اثلين كلايكول او البولاكزامر هي كلالتي 59.7, 5.8 195.8 M^{-1}

كاستنتاج لهذه الدراسة فان طريقة ذوبان الكانديسارتان بوجود البيتا السايكلودكسترن كانت على طبقا لمعدلة Higuchi's والان الذوبانية هي من نوع 1:1 . تاثير مساعد المذيب البولي اثلين كلايكول 400 او البوليمر بولوكزامر واضح . ان معدل الثباتية للمعقد بوجد البولير قد ازداد بشكل واضح ولكن بوجود المساعد المذيب قد قلت بشكل واضح .

INTRODUCTION

Inclusion complexes system of binary systems of cyclodextrin (CD)/drug have been well explored to enhance the dissolution of hydrophobic molecules(1). The low aqueous solubility and slow dissolution because of lipophilic and practically insoluble in water which may lead to irreproducible clinical response or therapeutic failure. A variety of solubilization techniques have been widely used, among these techniques are cosolvency and CD addition which are applied for non-polar solutes. CDs are able to form both inclusion and non-inclusion complexes(2). In addition, CDs and their complexes form water soluble aggregates in aqueous solutions. These aggregates are able to solubilize lipophillic water-insoluble drugs through non-inclusion complexation or micelle-like structures(3). Usage of CDs in pharmaceutical dosage forms has some limitation by their relatively high cost and due to problems of formulation and

principally related to the large amount necessary to obtain the desired drug-solubilizing effect(4). Some CDs are reported to have significant renal toxicity(5). Candesartan is used orally for treatment of hypertension due to possessing a competitive antagonist of the angiotensin II receptor(6).

In early 1990s, it was believed that cosolvents reduced the solubilization capacity of CDs. The solubility of testosterone with hydroxypropyl-β-CD was reported to be lower in the presence of

80% ethanol(7). However, in recent years, polymers have been reported to improve the solubilization capacity of CDs. A synergism be-tween CDs and water-soluble polymers in solubilizing naproxen was observed(8).

The high level of hydrogen bonding within water and furthermore has some properties like a sizable dielectric constant (80 at 20°C) and large surface tension (71 dynes/cm) makes water is as a good solvent. The structure of PEG-400 is H-(O-CH2-CH2)n-OH, where n is approximately 8 to 9. This unusual structure makes PEG miscible with water through hydrogen bonding. The hydrophobic hydrocarbon region helps to break the hydrogen bonding between water molecules, thus reducing overall intermolecular interactions(9).

The objective of this study is to find the synergistic effect of the cosolvent PEG 400 and the polymer poloxamer 188 on the aqueous solubility of (CC)- β-CD complex.

EXPERIMENTAL

MATERIALS

Candesartan Cilexetil was purchased from provizerpharma, India and Poloxamer 188 from HiMedia Laboratories, India. PEG 400 and ß-cyclodextrin was gifted by college of pharmacy, Baghdad University, Iraq.

PHASE SOLUBILITY METHOD

Phase solubility studies of (CC) were carried out according to Higuchi and Connors(10). Briefly, an excess amount of candesartan was added to 10 mL aqueous solutions containing range concentrations of either poloxamer 188 (0−4%, w/v), β-CD (0−1%, w/v) or PEG (0−50%,v/v) at 25±1 ºC separately. The mixtures of (CC) and polymers aqueous solution were shaken in a thermostated water bath at 25°C ± 2 for 24 h to reach equilibrium. After that, all the suspensions were filtered through 0.22 µm syringe filter and assayed for (CC) by UV Spectrophotometer (Sco tech, spuv-26, Germany) at the maximum absorbance wavelength of 255 nm. The phase solubility diagrams were plotted with rate (CC) solubility versus either ß-CD, poloxamer or PEG 400 concentration. Same procedure for phase solubility was done for mixtures of excess amount of drug in the presence of 0.4% of ß-CD in 10 mL aqueous solutions at 25±1 ºC containing different concentrations of poloxamer 188 or PEG 400.

The value of the stability constant ($Ks_{(1:1)}$) is used to compare the affinity of drugs for ß-CD alone or in the presence of PEG or poloxamer according to Equation (1).

$$Ksp_{(1:1)} = Slope / S_0 (1- Slope) \ldots\ldots\ldots (1)$$

Where S_0 represents the solubility of the drug and slope is the slope of the linear phase solubility curve. It is obvious that the value of $K_{Sp(1:1)}$ depends strongly on the value of S_0, which is defined as the drug solubility in the aqueous polymer solution when no cyclodextrin is present.

RESULT AND DISCUSSION

The hydrophilic polymers tend to have solubility enhancement effect on poorly soluble drugs via formation of weak water soluble complexes. It was found that the solubility of (CC) increased with the increasing concentration of poloxamer as shown in figure 1. The

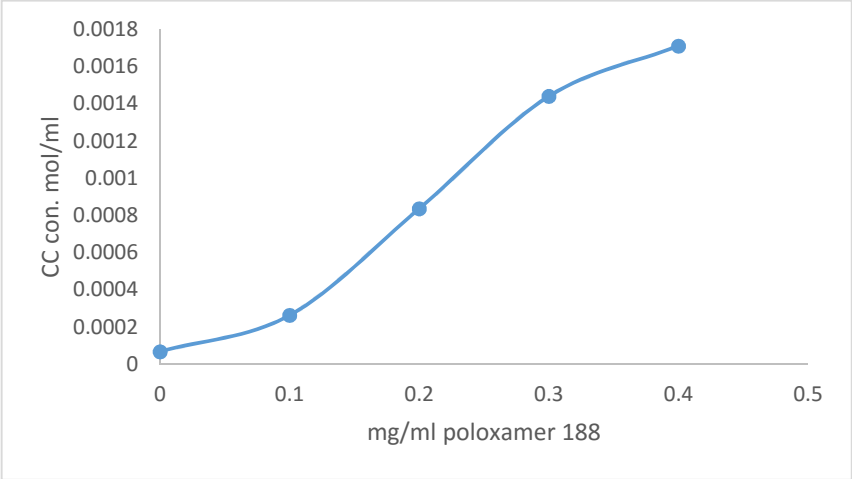

Figure 1: Aqueous solubility of (CC) diagram in the presence of (0.1-0.4 mg/ml) poloxamer 188 at 25±1 ºC

The increase in solubility with increasing poloxamer concentration indicates the solvent properties of poloxamer 188 for the drug. Poloxamer 188 causes a decrease of interfacial tension between the drug and dissolution medium. These results could be explained that the reduction in crystalline of drug led to a decrease of the energy required in the dissolving process and also to a highly dispersed state of the drug(11).

The solubility of (CC) in the presence of different concentrations of PEG 400 was increased with increase of PEG concentration as shown in Figure2. The co-solvent reduces strong water–water interactions and thereby reduces the ability of water to squeeze out non-polar solutes. Co-solvency was often considered at early stages due to its huge solubilization potential.

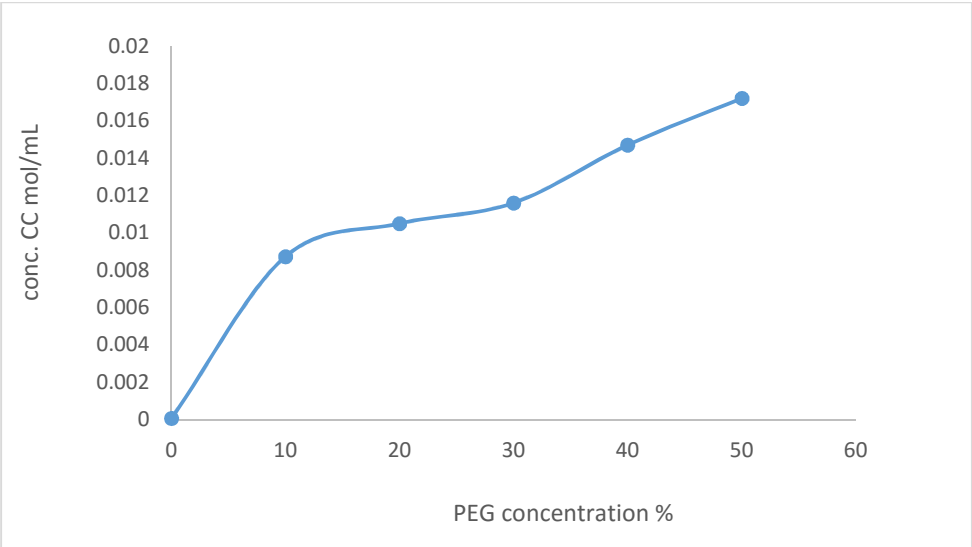

Figure 2: Aqueous solubility profile of (CC) in the presence of 10-50% PEG 400 at 25±1 ºC

The solubilizing effect of ß-CD toward (CC) demonstrated a significant increase in rate of drug solubility. The solubility of (CC) was linearly increased from 0.069 mg/mL to about 5.07 mg/ mL with the increasing of ß-CD concentrations from 0–1%, which could be attributed to the formation

of weak water-soluble complexes through intermolecular hydrogen bonding between ß-CD and candesartan celexitile as shown in Figure 3. The phase solubility curves of (CC) in aqueous solution at 25°C of ß-CD was of Higuchi's A_L-type confirming the formation of 1:1 complexes(1).
Factors, such as Van der Waals, hydrogen bonding, and hydrophobic forces, play important roles in forming a stable complex, it mainly depends on the CD cavity and the accessibility of the drug molecule to the CD cavity(12).

The effect of co-solvency of PEG on the solubility of (CC) in the presence of 0.04 mg / ml of ß-cyclodextrin was marked effect as shown Figure (4). It was found that with the increase of concentration of PEG 400 there was increase in the solubility of (CC). This result indicated that the solubility of CC was improved in the presence of PEG 400 as a co-solvent.

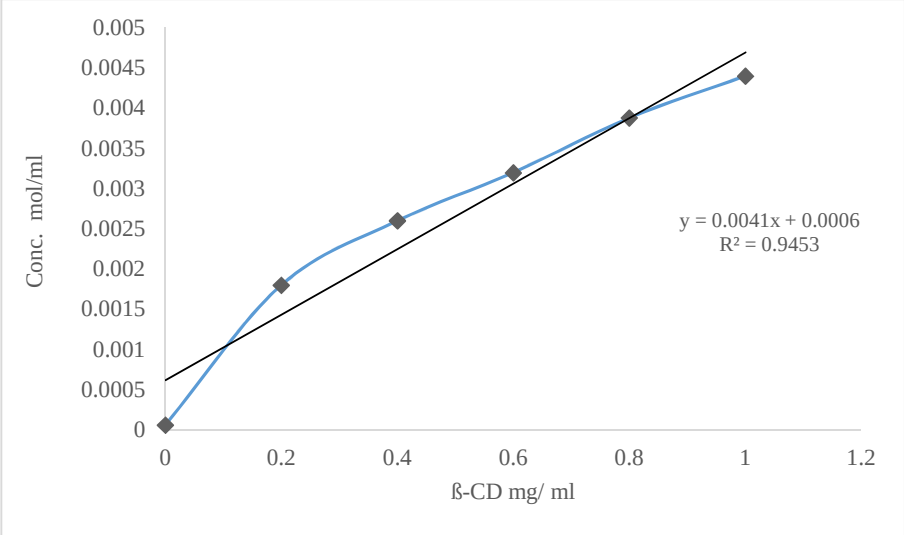

Figure 3: Aqueous solubility of (CC) in the presence of ß-CD at 25±1 ºC

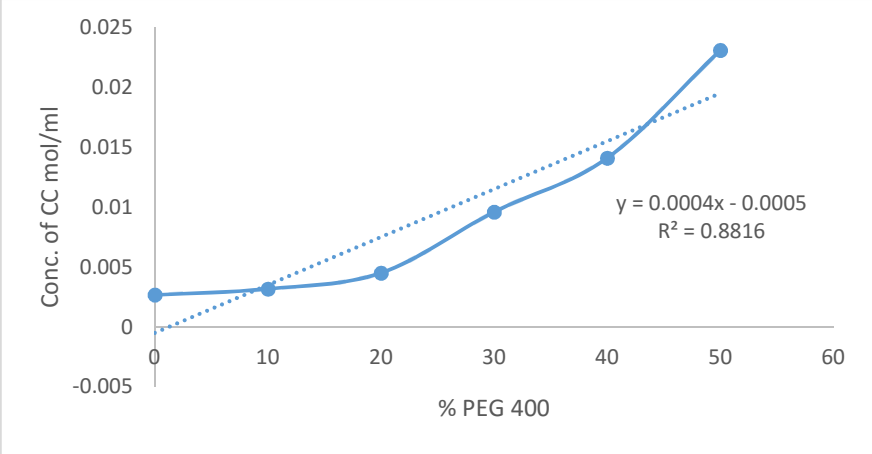

Figure 4: Aqueous solubility of (CC) in different concentration of PEG 400 and in the presence of 0.4 mg ß-CD at 25±1 ºC

The solubilizing effect of poloxamer 188 polymer on the solubility of CC in the presence of ß-CD showed increase of solubility of the CC with the increase of concentration of poloxamer 188 as shown in Figure 5. This result also indicated that the solubilizing effect of polymer had a marked effect on the solubility of CC in the presence of ß-CD.

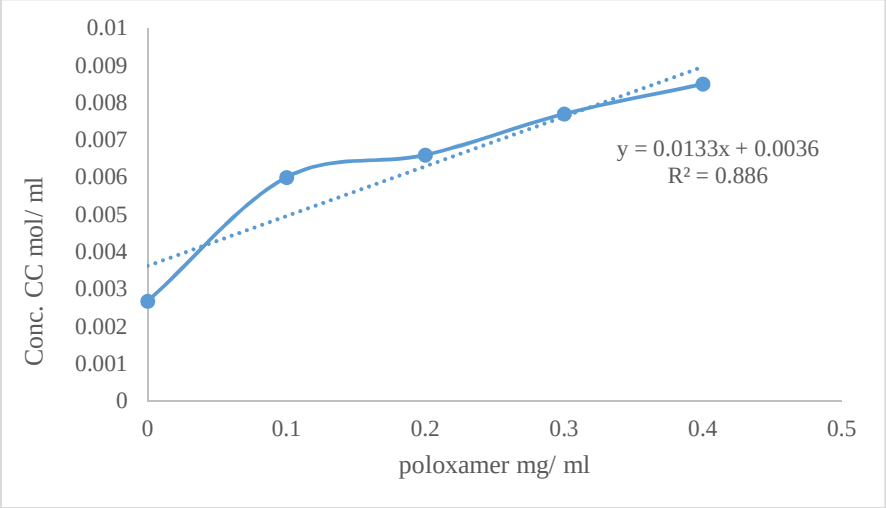

Figure 5: Aqueous solubility of (CC) in different concentration of poloxamer 188 and in the presence of 0.4 ß-CD at 25±1 ºC

The slopes in all cases were less than unity, thus confirming the formation of 1:1complexes(13). The values of stability constants (K*sp*) of CC-ß-CD complexes and in the presence of PEG 400 or poloxamer 188 with 0.4 mg / ml ß-CD are 59.7, 5.8 and 195.8 M^{-1} respectively. Addition of the polymer resulted in an increase in the stability constant, which could be attributed to the increase of the cyclodextrin complexing power towards CC. Addition of polymers could contribute to improvement of the complexation stability of cyclodextrins by establishing interactions such as hydrophobic bonds, Vander Waals dispersion forces, or hydrogen bonds and/or promoting the release of high-energy water molecules present in their cavity. Addition of co-solvent (PEG 400) showed a decrease of constant stability of the CC-CD complex which probably related to a competition between cyclodextrin and PEG 400 on interactions such as hydrogen bonds.

Conclusion

The effect of cosolvent, polymer and CD on the solubility profile of CC was significant. The solubility profile of CC in the presence of CD followed Higuchi equation confirming the formation of 1:1complexes. The synergism effect of the polymer on the CC-CD complexes was significant. The stability constant of the complexes was increased with polymer while showed reverse result with cosolvent.

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