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INTRODUCTION

The ion exchange resins are water insoluble cross-linked polymers carrying ion exchangeable groups. They have the ability to exchange their counter ions of equal charge for other counter ions in the surrounding medium. Therefore, ionized drugs can exchange for counter ions and attach to ion exchange resins, yielding "drug resin complex"[1]. The efficiency of drug loading depends on the properties of ion exchange resin and loaded drug. Among these factors, the solubility plays the most important role in drug loading on the ion-exchange resin since the loading cannot proceed without drug dissolving and ionization[2]. Therefore, low solubility critically limits drug loading onto ion exchange resin. The cyclodextrin inclusion complex can be applied for enhancement of drug solubility. From this advantage, cyclodextrins possibly have applicable potential for enhancing drug load in ion exchange resin by increasing drug solubility. Thus, this work was aimed to study the effect of cyclodextrin inclusion complex on drug resin complex. Ibuprofen, a class of non-steroidal anti-inflammatory drugs with poor aqueous solubility, was selected as model drug. Dowex® 1×2, styrene-divinylbenzene copolymer resin with dimethylamine functional group, was used as a representative of anionic exchange resins.

MATERIALS AND METHODS

Materials: Ibuprofen, β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) of molar substitution 0.6 and an anionic exchange resin in the chloride form (styrene-divinylbenzene copolymer resin with dimethylamine functional group (Dowex® 1x2-200)) were purchased from Sigma Chemical Co., USA. The rest reagents were analytical grade. Deionized water was used entirely in this work.

Phase solubility of ibuprofen cyclodextrin complexation: The cyclodextrin complexation of ibuprofen was studied by using phase solubility method according to Higuchi and Connors[3]. An excess amount of ibuprofen (200 mg) was weighed and placed in microcentrifuge tube containing various concentrations of cyclodextrin (in the range of 0-15 mM) at pH 6 and 8. The sample was placed and shaken in a horizontal shaker (30 rpm) at 25°C until the equilibrium was reached. Samples were collected and centrifuged to the quantification the dissolved drug using UV–visible spectrophotometry (NanoVue™, GE Healthcare, UK) at the wavelength of 222 nm. The stability constant of complex (K_c) was calculated according to the following equation: K_c = slope/ [S_0(1-slope)].Where slope is the slope of phase solubility diagram which plots between ibuprofen solubility expressed as molar concentration and cyclodextrin molar concentration, and S_0 is the drug solubility without cyclodextrin.

Stoichiometric characterization of inclusion complex: The stoichiometry of inclusion complex was determined by the phase solubility and continuous variation methods. The phase solubility method was conducted using the same procedure as above described, and the continuous variation method was performed according to Job[4]. Equal molar stock solutions of drug and cyclodextrin were prepared, and then proportionally mixed to obtain solutions containing various molar ratios of ibuprofen and cyclodextrin. The total concentration of these solutions was kept constant at 0.30 mM. After stirring for 24 h at 25 °C, the absorbance of drug solution was measured at the wavelength of 222 nm, and the difference in absorbance between the presence and absence of cyclodextrin, was plotted against molar fraction of drug (R).

The UV–visible spectra of ibuprofen solutions containing various concentrations of cyclodextrin (in the range of 0-15 mM) were recorded at 25°C from wavelengths of 200 to 400 nm. A drug solution without cyclodextrin was used as a control for this study. Cyclodextrin solutions at different concentrations were used as blank solutions.

The conductivity of ibuprofen solutions containing various concentrations of cyclodextrin (in the range of 0-15 mM) at pH 6 and 8 was measured using a conductivity meter (ECtestr11+, Eutech Instruments Pte Ltd, Singapore). The difference in conductivity of drug solutions between the absence and presence of cyclodextrin was determined.

Ibuprofen load in ion exchange resin: Firstly, saturated solutions of ibuprofen with and without cyclodextrin were prepared as follows. An excess amount of ibuprofen was added to phosphate buffer

solution at pH 6 with and without 15 mM cyclodextrin. The sample was vigorously shaken in a horizontal shaker (30 rpm) at 25 °C for 24 h. The samples were centrifuged and filtered through a 0.45-μm membrane filter to remove undissolved solid. The dissolved drug was assayed by UV–visible spectrophotometry. Drug loading was conducted by a single batch process. The saturated drug solutions with and without cyclodextrin were equilibrated with Dowex® 1x2 resin at 1:1 and 1:2 weight ratio of drug to resin, which was entirely performed on a horizontal shaker (30 rpm) at 25 °C. After equilibration, the drug solution was filtered through a 0.45-μm membrane filter and assayed by UV–visible spectrophotometry. The percentage of drug loading onto the resin was calculated by the following equation: % drug loading = $[(D_{IN}-D_{EQ})/W] \times 100$. Where D_{IN} and D_{EQ} is the drug content at initial and after equilibration, and W is the resin content used for drug loading.

Fixed concentration of loading solution: Drug solutions with and without 15 mM cyclodextrin were prepared at concentrations of 85 mM. These concentrations corresponded to the intrinsic solubility of the drugs. The drug solutions with and without cyclodextrin were equilibrated with Dowex® 1x2 resin at 1:1 weight ratio of drug to resin, and then performed with the same process as above described.

RESULTS AND DISCUSSION

Ibuprofen cyclodextrin complexation: The structure of ibuprofen presents hydrophobic properties of heterocyclic ring that can form the cyclodextrin inclusion complex, resulting in the solubility enhancement. The binding of ibuprofen within the cyclodextrin was a dynamic equilibrium that was reached at 2 h in both cases of β-CD and HP-β-CD. The ibuprofen concentration was constant after 2 h, which was determined to be the optimum equilibration time. The phase solubility diagram for ibuprofen and cyclodextrin systems is shown in Fig.1. In diagrams, the drug solubility increased with increasing the concentration of cyclodextrin, and thus the stability constant (K_c) could be calculated from the slope was 27.21 and 3.45 M^{-1} in the case of β-CD at pH 6 and 8, respectively while in the case of HP-β-CD complexes was 31.68 and 7.51 M^{-1} at pH 6 and 8, respectively. Obtained results demonstrated that pH and type of cyclodextrins influenced on the degree of inclusion complex formation and hence solubility. From Fig.1, the increase in pH, the solubility was increase regarding the ionization of ibuprofen. The pK_a of ibuprofen is 4.4. Therefore, the increase in drug solubility with raising pH from 6 to 8 could be explained by the increased ionization of drugs into anionic form. However, the increased pH resulted in the decreased stability constant (K_c). It implied that the inclusion complex formation to improve the solubility was less predominated at the higher pH. The stability constant of inclusion complex (K_c) with HP-β-CD was higher than that with β-CD, corresponding to the higher degree of apparent and relative solubility (Fig.1). It was possibly that the substituent hydroxylpropyl group of HP-β-CD decreased interactions with the aqueous environment and expanded the hydrophobic region, therefore increasing the formation of inclusion complex between drug and cyclodextrin via hydrophobic bonds[5].

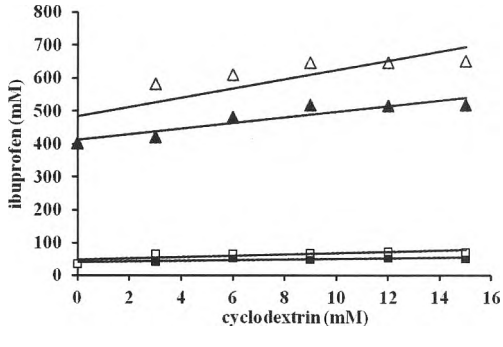

Figure 1 Phase solubility diagrams of ibuprofen at various pH: (■) pH6 β-CD, (□) pH 6 HP-β-CD, (▲) pH8 β-CD and (Δ) pH 8 HP-β-CD.

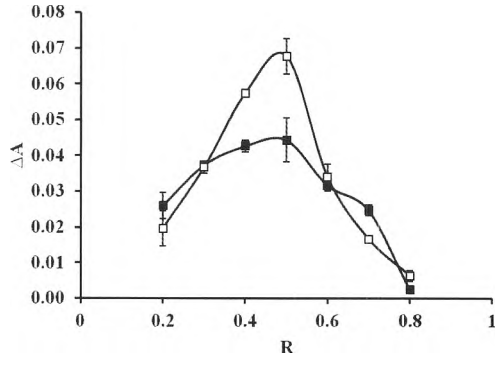

Figure 2 Continuous variation plots for ibuprofen and cyclodextrins system from absorbance measurements: (■) ibuprofen-β-CD and (□) ibuprofen-HP-β-CD.

Stoichiometry of inclusion complex: The inclusion complex of ibuprofen was characterized by the phase solubility and continuous variation methods. The phase solubility study showed that the drug solubility increased linearly with increasing the concentration of cyclodextrin (Fig.1). This identified A_L type in the inclusion complex formation. The slopes of the straight lines were less than 1, assuming 1:1 stoichiometric inclusion complex between drug and cylcodextrin[6]. According to the continuous variation method, the value of R where the difference in drug absorbance maximum indicated the stoichiometry of formed inclusion complex[7]. The results are shown in Fig.2. The obtained profiles exhibited a highly symmetrical shape in which the maximum difference in drug absorbance for both cyclodextrins was observed at R = 0.5, thus indicating the 1:1 stoichiometric inclusion was formed.

Figure 3 shows UV–visible spectra of ibuprofen in the presence and absence of cyclodextrin. The spectra of ibuprofen in the absence of cyclodextrin had maximum wavelength at 222 nm. In the presence of cyclodextrin, the spectra showed an increase in the absorption intensity (hyperchromic effect). The hyperchromic effect increased with increasing the concentration of cyclodextrin. Moreover, the spectra presented a shift of maximum peak to longer wavelength (bathochromic effect) when the cyclodextrin concentration was increased. These two effects resulted from cyclodextrin complexation by which the chromophore of drug was transferred from an aqueous medium to non-polar central cavity of cyclodextrin. With this regard, the molecular interaction between drug molecule and cyclodextrin accompanying with the exclusion of solvate water molecules induced structural modification and hence free movement of electrons onto different energy levels, finally causing the hyperchromic and bathochromic effect[8,9].

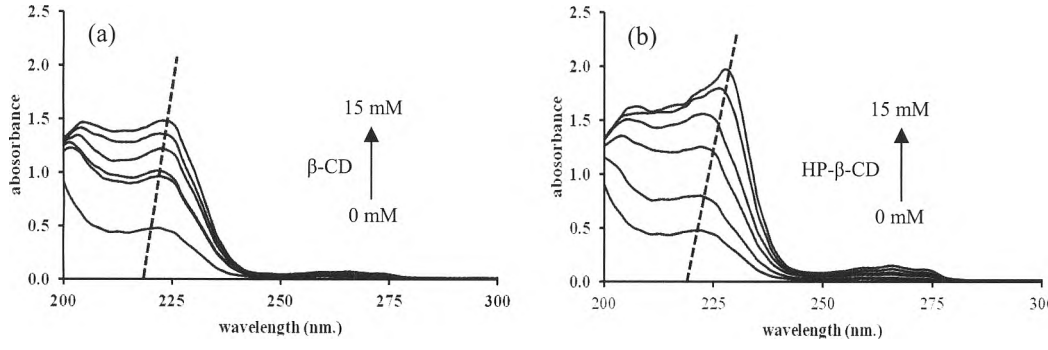

Figure 3 UV–visible spectra of ibuprofen solution containing cyclodextrin: (a) β-CD and (b) HP-β-CD.

Table 1 shows the difference of conductivity between the presence and absence of cyclodextrin. The presence of cyclodextrin exhibited a negative effect on the conductivity which decreased as increasing the concentration of both cyclodextrins. An increase in the different of conductivity was observed with increasing the concentration of cyclodextrin, thus affirming the evidence of interaction between drug and cyclodextrin[10]. With this, the included drug was expected to have less mobility than that of free drug and hence less effective as charge carrier[9,10]. The difference of conductivity also decreased when pH was raised. This supported the above finding that the stability of complex (K_c) decreased with increasing pH.

Table 1 The different conductivity of ibuprofen in the absence and presence of cyclodextrins.

	The different of conductivity (%)									
	β-CD (mM)					HP-β-CD (mM)				
pH	3	6	9	12	15	3	6	9	12	15
6	1.95	3.97	7.15	8.52	11.05	2.82	5.42	9.82	12.20	13.21
8	1.06	2.11	4.05	6.16	7.04	1.76	3.35	5.11	7.22	10.21

Preparation of ibuprofen-ion exchange resin complex: The loading of drug onto resin in the weight ratio of 1:1 and 1:2 was carried out at pH 6 by batch process[11]. Once the resin was placed in the loading solution the dissolved drug in ionized form (D^-) exchanged for counter ion (Cl^-), and bind the resin ($RN(CH_3)_3Cl$) via ion exchange reaction, forming resinate complex ($RN(CH_3)_3D$) until equilibrium. For preparation of drug resin complex, it is desirable to increase the loading efficiency in order to reduce loss of drug, use of excipients and minimize size of final dosage form[12].

Figure 4 presents drug loading onto ion exchange resin in the presence of 15 mM cyclodextrin, which was higher than that in the absence of cyclodextrin. The increased loading resulted from the increased solubility and hence concentration of drugs in loading solution. Drug load in resin was also influenced by the weight ratio of drug to resin. In the presence and absence of cyclodextrin, the loading of drug in resin at the weight ratio of 1:1 was higher than 1:2. This was due to the lower quantity of binding sites, thus resulting in more concentration and hence percentage of drug loaded in the resultant resinate complex.

Fixed concentration of loading solution: This part was proposed to study the influence of cyclodextrin on drug loading onto ion exchange resin. The concentration of drug in loading solution was fixed according to intrinsic solubility, which was 85 mM; while that of cyclodextrin was entirely fixed at 15 mM. The percentages of drug loading are shown in Fig.4. At equivalent drug concentration, the presence of both cyclodextrins i.e. β-CD and HP-β-CD had no effect on the extent of drug loading.

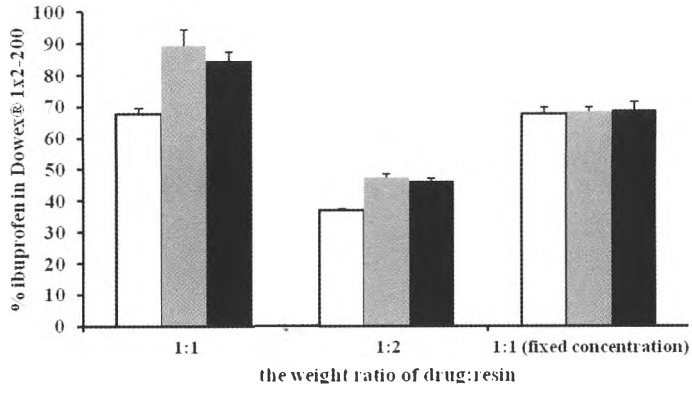

Figure 4 Percentage of ibuprofen load in Dowex® 1x2-200 at the weight ratio of drug:resin of 1:1, 1:2; (□) in the absence of cyclodextrin, in the presence of 15 mM (▨) β-CD and (■) HP-β-CD.

CONCLUSION

Ibuprofen successfully formed 1:1 stoichiometric inclusion complex with β-CD and HP-β-CD and their solubility was significantly enhanced. The solubility enhancement resulted from the inclusion complex formation of drug with cyclodextrin. Drug load in ion exchange resin in the presence of cyclodextrin was considerably increased due to the formed inclusion complex and hence increased solubility of loaded drug. This finding presented a novel application of cyclodextrin for help in preparing as drug delivery systems of poorly water-soluble drugs.

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REFERENCES

1. Srikanth MV, Sunil SA, Rao NS, Uhamwangho MU, Murthy KVR. 2010. Ion-exchange resins as controlled drug delivery carriers. J Sci Res. 2(3):597-611.
2. Anand V, Kandarapu R, Garg S. 2001. Ion-exchange resins: carrying drug delivery forward. Drug Discov Today. 6:905-914.
3. Higuchi T, Connors KA. 1965. Phase-solubility techniques. Adv Anal Chem Instrum. 4: 117-212.
4. Job P. 1928. Job's plot analyses for the 2-CG and 3-CG complexes were consistent with 1:1 stoichiometry. Ann Chim. 9:113-134.
5. Liu R. 2008. Water-Insoluble Drug Formulation. London: CRC Press. 133-154.
6. Obaidat AA, Khanfar RA, Khawam MN. 2009. The effect of β-cyclodextrin on the solubility and dissolution rate of meloxicam and investigation of the driving force for complexation using molecular modeling. J Incl Phenom Macrocycl Chem. 63:273-279.
7. Sinko PJ. 2011. Martin's physical pharmacy and pharmaceutical sciences. London: Lippincott Williams & Wilkins. 197-222.
8. Singh R, Bhart N, Madan J, Hiremath SN. 2010. Characterization of cyclodextrin inclusion complexes: A review. J Pharm Sci&Tech. 2(3):171-183.
9. Mehta SK, Bhasin KK, Dham S. 2008. Energetically favorable interactions between diclofenac sodium and cyclodextrin molecules in aqueous media. J Colloid Interf Sci. 326:374-381.
10. Cabaleiro-Lago C, Nilsson M, Valente AJM, Bonini M, Söderman O. 2006. NMR diffusometry and conductometry study of the host–guest association between β-cyclodextrin and dodecane 1,12-bis(trimethylammonium bromide). J Colloid Interf Sci. 300:782-787.
11. Irwin WJ, Belaid KA, Alpar HO. 1987. Drug-delivery by ion-exchange. Part III: Interaction of ester prodrug of propranolol with cationic exchange resins. Drug Dev Ind Pharm. 13:2047-2066.
12. Jeong SH, Park K. 2008. Drug loading and release properties of ion-exchange resin complexes as a drug delivery matrix. Int J Pharm. 361:26-32.