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Gefitinib–cyclodextrin inclusion complexes: physico-chemical characterization and dissolution studies

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Abstract

Background: Gefitinib, an anticancer drug, has an extremely low aqueous solubility, and its oral absorption is limited by its dissolution rate. The solubility and dissolution of gefitinib can be improved by complexation with cyclodextrins (CDs). *Methods:* Phase solubility studies of gefitinib with hydroxypropyl βCD (HPβCD) and randomly methylated βCD (RMβCD) in *n* various aqueous systems was conducted to characterize the complexes in the liquid state. The inclusion complexes in the solid state were prepared by freeze-drying method and characterized by X-ray diffractometry (X-RD) and differential scanning calorimetry (DSC). *Results:* Gefitinib formed stable complexes with HPβCD and RMβCD in distilled water as indicated by the association rate constants (Ks) of 458.9 and 1096.2 M^{-1} for HPβCD and RMβCD, respectively. The complexation of gefitinib with CDs in pH 4.5 acetate buffer indicated an A_N type of phase-solubility diagrams, whereas gefitinib and HPβCD in distilled water in the presence of polymers such as polyvinyl pyrrolidone K-30 (PVP) or hydroxypropyl methylcellulose E3 (HPMC) resulted in A_P-type phase-solubility diagrams. The solid-state amorphous complexes (as described by DSC and X-RD) showed substantial increases in the solubility and dissolution rate of gefitinib with both CDs. Further increases in the solubility and dissolution rate of the gefitinib-HPβCD freeze-dried complex were obtained by physically mixing the complex with PVP and HPMC. *Conclusion:* Gefitinib formed stable inclusion complexes with HPβCD and RMβCD, and the solubility and dissolution rate of the drug was significantly increased.

Key words: *Cyclodextrins; dissolution rate; gefitinib; inclusion complex; solubility*

Introduction

Gefitinib is an anilinoquinazoline (*N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine) with a molecular mass of 446.9 Da (http://www.drugbank.ca/drugs/DB00317). It is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor used in the treatment of locally advanced non-small cell lung cancer[1]. It is a lipophilic dibasic compound with pK_a values of 5.28 and 7.17 and, accordingly, exhibits a pH-dependent solubility in gastrointestinal fluid (http://www.fda.gov/cder/foi/label/2005/021399s008lbl.pdf). Gefitinib undergoes rapid dissolution in acidic media, but the solubility drops as pH increases to neutral intestinal pH. Based on the intestinal permeability data of gefitinib in a Caco-2 model, the solubility (and dissolution rate) of gefitinib along the intestine was considered as the rate-limiting step in the absorption process[2,3]. Gefitinib has been categorized as a Biopharmaceutical Classification System (BCS) class II compound, as the intestinal permeability is high and the solubility (and dissolution rate) is low along the intestine[4,5]. The oral bioavailability following a single dose of 250 mg gefitinib (Iressa® tablet) as the free base in healthy male volunteers was 57%. An increase in gastric pH above 5 resulted in a 47% reduction of the

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relative bioavailability[6]. The bioavailability could be greatly increased by improving the solubility and dissolution of the drug. This would allow a reduction in dose and oral dose-related side effects, such as diarrhea and vomiting[1,4].

Cyclodextrins (CDs) are crystalline, cyclic oligosaccharides with a bucket-like structure having a hydrophobic internal cavity and a hydrophilic exterior. The interior of the toroid is hydrophobic as a result of the electron-rich environment provided in large part by the glycosidic oxygen atoms. The structure of CD allows the formation of inclusion complexes in which lipophilic compounds are noncovalently bound within the cavity. CDs have been employed in the pharmaceutical industry to increase the aqueous solubility and stability of drugs in both parenteral and oral drug delivery systems[7–9]. The promising advantages of β-cyclodextrin (β-CD) as a drug carrier are limited by its low aqueous solubility (1.8 g/100 mL). Chemical modification of β-CD can produce products of very high water solubility (>50 g/100 mL) with minimal toxicity and greater inclusion ability[10]. More than 1500 CD derivatives have now been reported and more than 100 are available as fine chemicals, but only a very few are available as pharmaceutical grade excipients[10]. Two examples of highly water-soluble β-CD derivatives are hydroxypropyl-β-CD (HP-β-CD) and randomly methylated-β-CD (RM-β-CD). These have the best balance of enhanced aqueous solubility (>50 g/100 mL) and range of drugs which can form stable complexes. Based on molecular size and structure, we hypothesized that gefitinib could form stable inclusion complexes with CDs in the liquid and solid states to improve the solubility and dissolution of this drug for enhanced absorption and oral bioavailability. The objective of this investigation was to characterize the complexation of gefitinib with HP-β-CD and RM-β-CD in the liquid state through the use of phase solubility diagrams. Solid state complexation was examined through differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and the improvement in solubility and dissolution rate of the solid drug complex. In addition, the influence of physically mixing polyvinyl pyrrolidone (PVP) K-30 or hydroxypropyl methylcellulose (HPMC) E3 with the gefitinib–HP-β-CD freeze-dried complex on the dissolution rate of gefitinib is reported.

Materials and methods

Materials

Gefitinib was from Sequoia Research Products Ltd. (Pangbourne, UK). Glacial acetic acid was from Fisher Scientific (Suwannee, GA, USA). PVP K30 was obtained from ISP Inc. (Wayne, NJ, USA), while HP-β-CD and RM-β-CD were obtained from Cyclodextrin Technologies Development, Inc. (High Springs, FL, USA). HPMC E3 grade was obtained from Dow Chemicals (Midland, MI, USA).

Phase solubility studies

Phase solubility studies *in distilled water and pH 4.5 acetate buffer* were conducted according to the method of Higuchi and Connors[11]. Approximately 5 mg quantities of gefitinib were added to a series of glass vials containing 2.0 mL of distilled water or pH 4.5 acetate buffer. Increasing amounts of each CD (HP-β-CD or RM-β-CD) were then placed in each sample. These suspensions were sonicated five times for 30 minutes with 1-hour intervals to ensure equilibrium solubility of gefitinib in solution. The samples were then filtered through a 0.22-μm membrane filter (Millipore, Billerica, MA, USA). The filtered samples were analyzed by UV spectrophotometry at 340 nm (DU460; Beckman Coulter, Fullerton, CA, USA). Solubility diagrams were constructed by plotting the molar concentration of gefitinib dissolved (solubility) versus the molar concentration of the CD. From these diagrams the stability rate constants for the complexation of gefitinib with CDs were calculated.

The effect of polymers (PVP and HPMC) on the phase solubility of gefitinib with HP-β-CD was also investigated. A series of vials containing 2.0 mL of distilled water and 5 mg of gefitinib and increasing amounts of HP-β-CD, as described above, were prepared. To each vial, PVP or HPMC at 25% of HP-β-CD was added. The phase solubility studies were conducted as described above.

The UV spectrophotometric method for gefitinib was validated. The calibration curve was linear in the working range of 2–20 μg/mL with a slope of 0.045 (r^2 = 0.9998) and 0.034 (r^2 = 0.9999) in pH 4.5 acetate buffer and distilled water, respectively. The presence of different concentrations of either HP-β-CD or RM-β-CD had a negligible effect on the absorbance of gefitinib at 20 μg/mL at 340 nm.

Formulation of solid gefitinib–cyclodextrin complexes

The kneaded formulations (250 mg each) were prepared in a 1:1 gefitinib:CD molar ratio using either HP-β-CD or RM-β-CD. The CD and gefitinib were wetted with a few drops of distilled water and kneaded in a mortar for 30 minutes. The product was then dried at 37°C for 24 hours, powdered, and stored in sealed glass vials.

The freeze-dried formulations were prepared in both 1:1 (250 mg each) as well as 1:2 (300 mg each) gefitinib:CD ratios. In order to ensure that both gefitinib and the CD are in solution for freeze drying, 30 mL of approximately 0.5 M acetic acid solution was added to each

formulation. Each formulation was then frozen at –70°C and freeze-dried for approximately 48 hours (FreeZone 4.5; Labconco, Kansas City, MO, USA). The freeze-dried samples were stored in sealed glass vials.

Powder X-ray diffractometry

The powder X-ray diffractometry (XRD) patterns of gefitinib, CDs, and their formulations were recorded using an automated Philips X'Pert X-ray diffractometer (Almelo, the Netherlands). Samples were irradiated with monochromatized Cu-Kα radiation and analyzed between 2θ angles of 10 and 60. The voltage, current, and time per step used were 40 kV, 55 mA, and 1 second, respectively.

Differential scanning calorimetry

Gefitinib and its complexes with HP-β-CD and RM-β-CD were analyzed by differential scanning calorimeter (Q200 DSC; TA Instruments, New Castle, DE, USA). The samples (~5 mg) were sealed using aluminum pans and scanned at 10°C/minute between 40°C and 160°C at a frequency modulation of 60 Hz. The thermograms were analyzed with the Universal Analysis Software (version 4.0C) provided with the instrument.

Dissolution studies

Dissolution experiments were performed at 37°C on a SRII 6-Flask Dissolution Test Station (Hanson Research, Chatsworth, CA, USA) according to the dispersed amount method[12]. Approximately 0.025 moles of gefitinib or the CD formulation (kneaded mixture or freeze-dried formulation) equivalent to 0.025 moles of gefitinib was added to 1 L of water in a dissolution vessel at a stirring speed of 50 rpm. At fixed time intervals (5, 10, 15, 20, 30, 60, 90, 120, 180, and 240 minutes), 10 mL samples were drawn with a filter syringe and the gefitinib content was determined spectrophotometrically as in the phase solubility studies. A correction was applied for the cumulative dilution caused by replacement of the sample with an equal volume of fresh medium. After obtaining preliminary results, additional formulations were made using a physical mixture of 10% (w/w) and 25% (w/w) PVP or HPMC and the freeze-dried HP-β-CD formulation. Each study was repeated three times using sample sizes containing an equivalent amount of gefitinib in each formulation. The dissolution profiles were evaluated on the basis of the dissolution efficiency parameter at 30 minutes ($DE_{30\ minutes}$, %) and at 240 minutes ($DE_{240\ minutes}$, %) calculated from the area under the dissolution curves and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time[13].

Statistical analysis

The differences between multiple groups of the dissolution efficiency data ($DE_{30\ minutes}$ and $DE_{240\ minutes}$) were assessed by analysis of variance (ANOVA) followed by Tukey's post test to determine the level of significance between various groups. Mean differences with $P < 0.05$ were considered to be significant.

Results and discussion

Inclusion complexation in the liquid state

Phase solubility studies. The phase solubility diagram of gefitinib as a function of the concentration of various CDs at room temperature is shown in Figure 1. The increase in solubility of gefitinib in water with an increase in concentration of the CDs indicates an A_L type of phase solubility diagram. The initial increase in solubility of gefitinib in pH 4.5 acetate buffer with CDs and a negative deviation linearity in the solubility curve indicate an A_N type of phase solubility diagram[11]. An apparent 1:1 stability constant (K_s) of the complex was calculated from the slope (R) and intercept (S_0) of the linear portion of the phase solubility diagram according to the equation:

$$K_s = \frac{R}{S_0(1-R)}$$

The K_s values of the gefitinib–HP-β-CD and gefitinib–RM-β-CD complexes derived from the phase diagram of the study with distilled water were 458.9 and 1096.2 M^{-1}, respectively. The K_s values of gefitinib–CD complexes seem suitable for practical application in terms of improving the dissolution rate-limited gastrointestinal absorption and oral bioavailability[7]. If the complex were too weak, there is little improvement in the solubility of the drug. On the other hand, if the complex was too strong, as indicated by a stability constant greater than 10,000 M^{-1}, the complex could not dissociate easily and oral absorption of the complex is not possible[7]. Only drug that is dissociated from the CD complex is absorbed. The K_s values of the gefitinib–HP-β-CD and gefitinib–RM-β-CD complexes derived from the phase diagram of the study with pH 4.5 acetate buffer were 71.4 and 102.5 M^{-1}, respectively. These values indicate that CDs form a weak inclusion complex with gefitinib at a pH 4.5. In this study, the solubility of gefitinib in the presence of RM-β-CD increased more than in the presence of HP-β-CD in both distilled water and pH 4.5 buffer. The complexing ability and, therefore, solubility improvement by RM-β-CD is generally higher than HP-β-CD for many drug molecules, for example, acitretin[14],

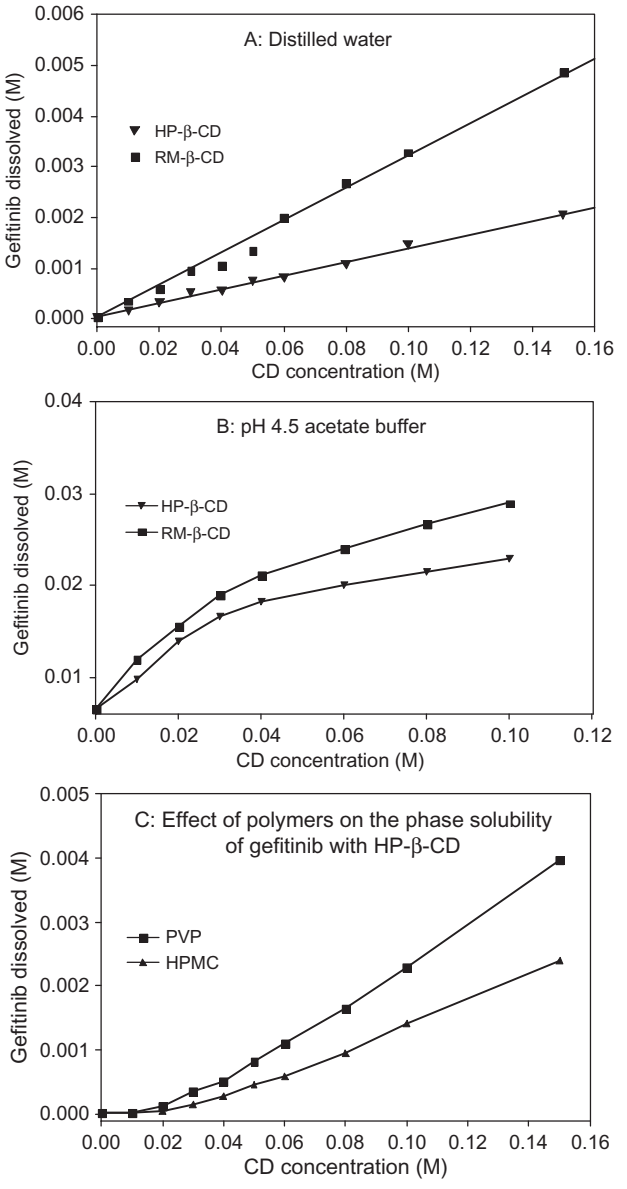

Figure 1. Phase solubility diagrams of gefitinib with HP-β-CD and RM-β-CD in various solvent systems at room temperature (~25°C).

bupranolol[15], and benzodiazepine compounds[16]. In the presence of polymers, HP-β-CD demonstrated an A_P type of phase solubility diagram (positive deviation from linearity) as shown in Figure 1c. Both PVP and HPMC increased the solubility of gefitinib by 2- and 1.5-folds, respectively, as compared to HP-β-CD alone. The A_P type phase solubility diagram indicates the formation of ternary complexes.

Inclusion complexation in the solid state

The inclusion complexes of gefitinib with CDs were prepared and characterized in the solid state. The CD freeze-dried formulations and the kneaded mixtures were analyzed to determine if inclusion complexes were formed by each method of preparation. The existence of a gefitinib–CD complex in the solid state was confirmed by powder XRD and DSC. The XRD of samples made with HP-β-CD and RM-β-CD are shown in Figures 2 and 3, respectively. Powder XRD is a useful method for the detection of CD complexation in powder or microcrystalline states[17]. The diffraction pattern of the complex should be clearly distinct from those of the superposition of each component if a true inclusion

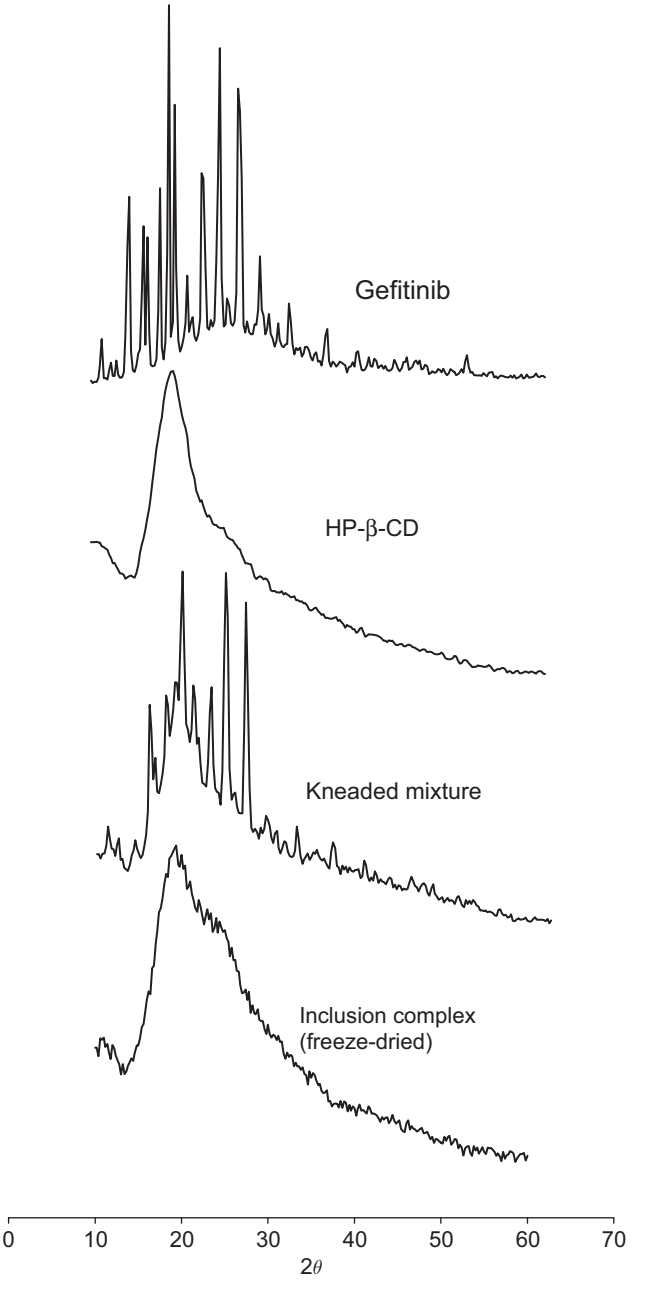

Figure 2. X-ray diffraction analysis of gefitinib, HP-β-CD, their kneaded mixture (1:1), and freeze-dried formulation (1:1).

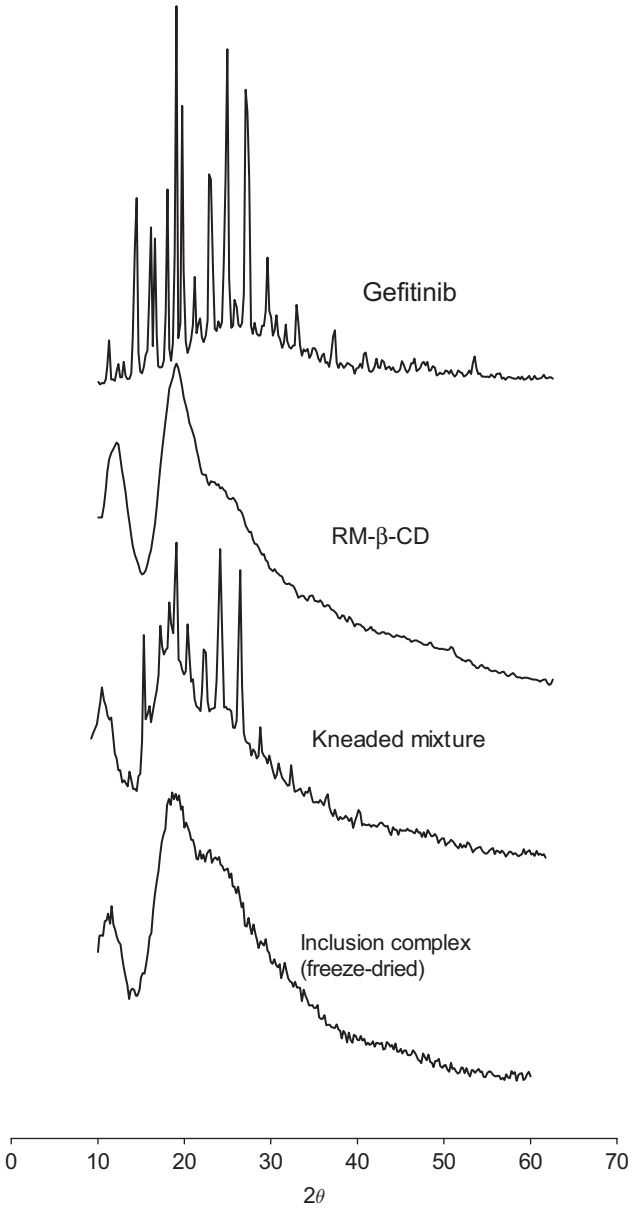

Figure 3. X-ray diffraction analysis of gefitinib, RM-β-CD, their kneaded mixture (1:1), and freeze-dried formulation (1:1).

complex exists. The inclusion process may increase the amorphous character and can also be explained based on the procedure employed to obtain the complex[18].

The XRD pattern of gefitinib revealed several high-intensity reflections corresponding to the diffraction peaks 18.6°, 19.2°, 24.2°, 26.2°, and 26.4° (2θ). The strong diffraction peaks of gefitinib indicate the crystalline nature of the drug. A hollow pattern was recorded for HP-β-CD and RM-β-CD demonstrating their amorphous states as evidenced from the absence of diffraction peaks in Figures 2 and 3, respectively. Similarly, complete drug amorphousness was detected in the diffraction patterns of the freeze-dried formulations. These have a typical flat behavior that confirms the strong ability of the amorphous carriers HP-β-CD and RM-β-CD to induce an amorphous nature in gefitinib. The characteristic gefitinib peaks are completely absent in the inclusion complexes of gefitinib with HP-β-CD and RM-β-CD, whereas some of these peaks are evident in the kneaded mixtures of gefitinib with the CDs. This indicates that the gefitinib–CD inclusion complexes constitute a new solid state.

More direct evidence of complex formation was obtained from DSC thermograms for HP-β-CD and RM-β-CD complexes as shown in Figures 4 and 5, respectively. Gefitinib shows an endothermic peak corresponding to its melting point (~196°C). The kneaded mixtures of gefitinib with HP-β-CD and RM-β-CD also show the endothermic peak that is characteristic of gefitinib. This indicates that there was not complete interaction of gefitinib with HP-β-CD and RM-β-CD on kneading. For inclusion complexes the characteristic melting point peak of gefitinib almost completely disappeared, showing an interaction of gefitinib with HP-β-CD and RM-β-CD. These results indicate that the inclusion complexes prepared by freeze drying exist in the new solid state[19].

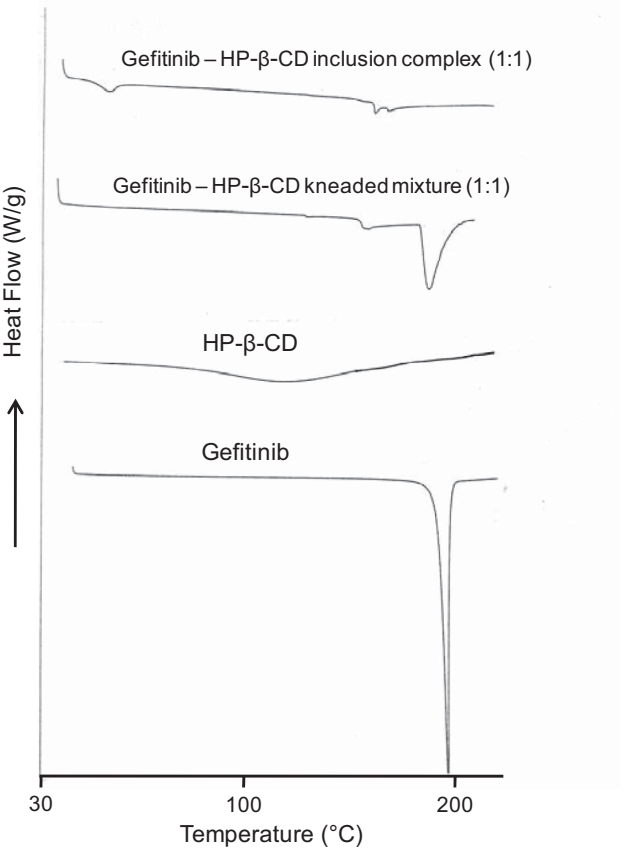

Figure 4. Differential scanning calorimetry analysis of gefitinib, HP-β-CD, their kneaded mixture (1:1), and freeze-dried formulation (1:1).

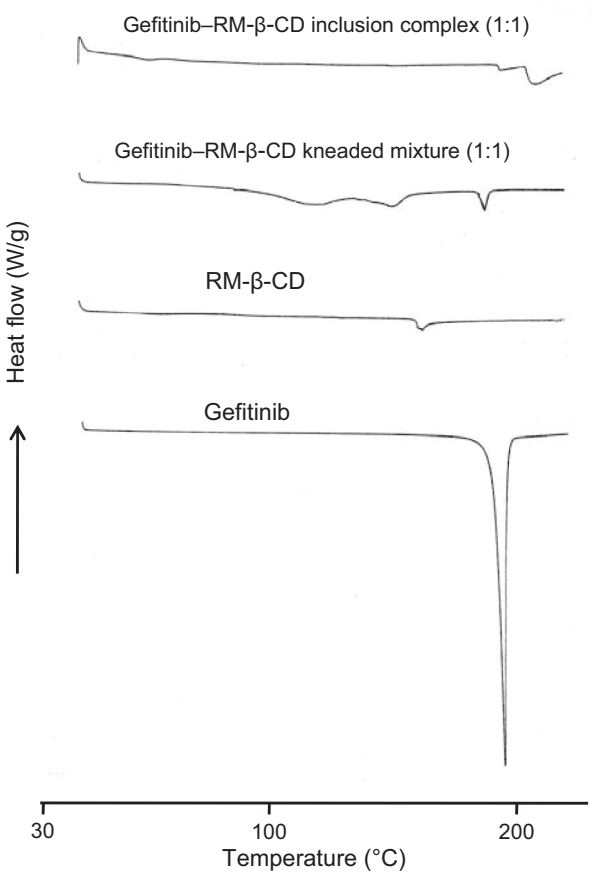

Figure 5. Differential scanning calorimetry analysis of gefitinib, RM-β-CD, their kneaded mixture (1:1), and freeze-dried formulation (1:1).

Dissolution studies

Dissolution studies on various gefitinib–CD systems were conducted to demonstrate the effect of complexation and the addition of polymers on the dissolution rate of gefitinib. For their evaluation, two parameters, dissolution efficiency calculated at 30 minutes and at 240 minutes ($DE_{30\ minutes}$ and $DE_{240\ minutes}$), were measured for all products studied (Table 1). The dissolution profiles of gefitinib and various binary systems of HP-β-CD are shown in Figure 6. The kneaded mixture showed little improvement in the dissolution of the drug. The HP-β-CD inclusion complex (1:1) showed rapid dissolution; about 50% of the drug dissolved in 30 minutes. The $DE_{30\ minutes}$ and $DE_{240\ minutes}$ were about 3 and 2-folds, respectively, higher than the kneaded mixture ($P < 0.05$). The HP-β-CD inclusion complex (1:2) showed much higher dissolution (65% dissolution in 240 minutes) compared to gefitinib alone. The $DE_{30\ minutes}$ and $DE_{240\ minutes}$ were about 5- and 3-folds, respectively, higher than the kneaded mixture ($P < 0.001$).

Table 1. Effect of CDs and polymers on the dissolution efficiency of gefitinib.

Product	Dissolution efficiency (0–30 min.)	Dissolution efficiency (0–240 min.)
Effect of HP-β-CD gefitinib		
Gefitinib	6.92 ± 1.890	15.35 ± 3.597
Kneaded mixture	14.83 ± 6.360	21.89 ± 8.582
Inclusion complex (1:1)	46.00 ± 5.940**	49.83 ± 6.144**
Inclusion complex (1:2)	67.66 ± 4.160***	69.88 ± 3.333***
Effect of RM-β-CD gefitinib		
Gefitinib	6.92 ± 1.890	15.35 ± 3.597
Kneaded mixture	16.39 ± 4.614	21.22 ± 5.313
Inclusion complex (1:1)	34.33 ± 4.279**	40.64 ± 4.576**
Inclusion complex (1:2)	74.50 ± 1.629***	72.25 ± 2.962***
Effect of polymers on HP-β-CD complex[a]		
PVP 10% (w/w)	75.17 ± 1.453***	81.79 ± 2.636***
PVP 25% (w/w)	84.50 ± 2.249***	90.58 ± 3.321***
HPMC 10% (w/w)	79.83 ± 4.090***	85.42 ± 3.385***
HPMC 25% (w/w)	87.20 ± 1.630***	93.92 ± 2.977***

[a]Added to 1:1 inclusion complex of HP-β-CD.
**$P < 0.01$ and ***$P < 0.001$ versus gefitinib.

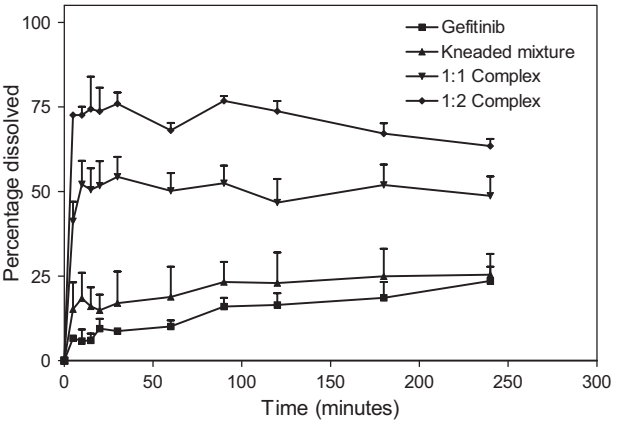

Figure 6. Dissolution of gefitinib–HP-β-CD formulations in distilled water. Values represent mean ± SD, $n = 3$.

The dissolution profiles of gefitinib and various binary systems of RM-β-CD are shown in Figure 7. As with HP-β-CD, the kneaded mixture of RM-β-CD showed slight improvement in the dissolution of the drug. The RM-β-CD inclusion complex (1:1) showed much higher dissolution; about 40% of the drug dissolved in 10 minutes, and the total amount of drug dissolution in 240 minutes was ~40% which is 2-fold higher than the kneaded mixture. The $DE_{30\ minutes}$ and $DE_{240\ minutes}$ of the 1:1 complex were also about 2-fold higher than the kneaded mixture ($P < 0.05$). The 1:2 complex showed substantially higher dissolution (70% dissolution in 240 minutes) compared to gefitinib alone. The $DE_{30\ minutes}$ and $DE_{240\ minutes}$ were

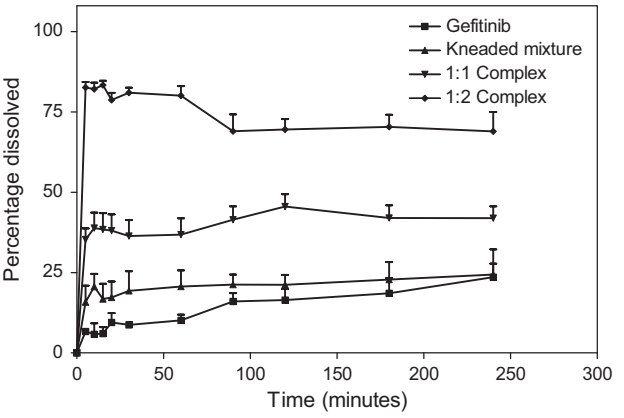

Figure 7. Dissolution of gefitinib–RM-β-CD formulations in distilled water. Values represent mean ± SD, $n = 3$.

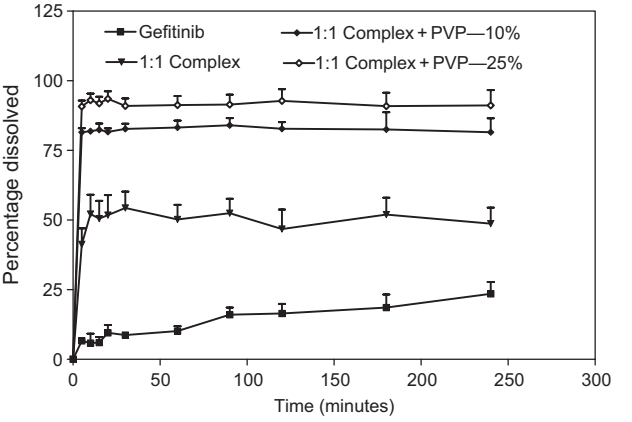

Figure 8. Effect of PVP on the dissolution of gefitinib–HP-β-CD complex in distilled water. Values represent mean ± SD, $n = 3$.

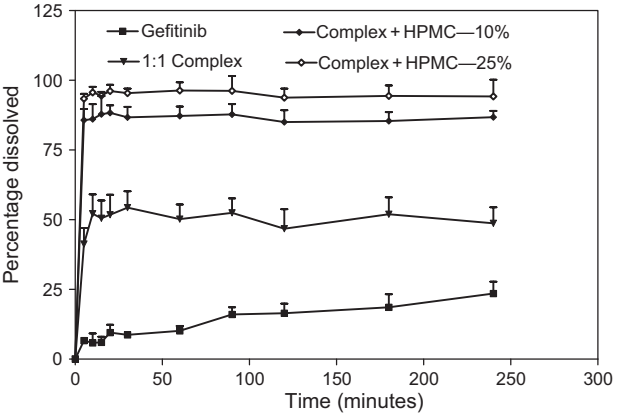

Figure 9. Effect of HPMC on the dissolution of gefitinib–HP-β-CD complex in distilled water. Values represent mean ± SD, $n = 3$.

4.5 and 3.5-folds higher, respectively, than the kneaded mixture ($P < 0.001$).

It is apparent that both HP-β-CD and RM-β-CD complexes at a 1:2 ratio rapidly dissolved and maintained a high supersaturated concentration. The fast dissolution of gefitinib followed by supersaturation may be attributable to the amorphous complex formation of the drug with these CDs. The decrease in the drug concentration after 1 hour may be because of the dissociation of the complex, resulting in precipitation of gefitinib crystals[20]. The freeze-dried complexes showed improved dissolution relative to the kneaded mixtures with both CDs. This suggests formation of an inclusion complex by freeze drying with a reduction of the crystallinity of the products as confirmed by X-ray diffraction studies.

Since the phase solubility diagrams indicated the formation of a 1:1 drug:CD complex, the addition of a hydrophilic polymer to these complexes may result in better dissolution than the use of a 1:2 ratio of drug:CD. The gefitinib–HP-β-CD inclusion complex (1:1) was chosen for these studies based on the $DE_{30\ minutes}$ and $DE_{240\ minutes}$ results (Table 1). Two hydrophilic polymers, PVP and HPMC were individually physically blended at 10% (w/w) and 25% (w/w) concentrations with the gefitinib–HP-β-CD inclusion complex (1:1). The dissolution profiles of these blends containing PVP and HPMC as co-solubilizers are shown in Figures 8 and 9, respectively. The addition of hydrophilic polymers to the CDs provided a synergistic effect on increasing the dissolution of gefitinib. The gefitinib–HP-β-CD (1:1) complex yielded about 50% dissolution in 30 minutes, whereas 10% (w/w) and 25% (w/w) PVP in association with the complex increased the dissolution to about 80% and 90%, respectively. The $DE_{240\ minutes}$ values achieved by 10% (w/w) and 25% (w/w) PVP products were 1.6- and 1.8-folds higher, respectively, than the 1:1 complex ($P < 0.001$). Similarly, addition of HPMC at 10% (w/w) and 25% (w/w) to the complex increased the dissolution to about 85% and 95%, respectively, in 30 minutes. The $DE_{240\ minutes}$ values achieved by PVP 10% (w/w) and 25% (w/w) products were 1.7 and 1.8-folds higher, respectively, than the 1:1 complex ($P < 0.001$). Similar results were reported for celecoxib–HP-β-CD systems containing hydrophilic polymers[21,22]. The polymers provided enhanced dissolution probably through (1) enhancement of the complexation of drug, (2) increased solubilization efficiencies of HP-β-CD, and (3) stronger reduction of drug crystallinity and better inclusion caused by the combined action of HP-β-CD and the hydrophilic polymers.

Conclusions

The complexation of gefitinib with CDs in the liquid and solid states was determined. The liquid state complexation

(in water and pH 4.5 acetate buffer) was determined by phase solubility diagrams. These indicated stable inclusion complexes with association rate constants (K_s) of 458.9 and 1096.2 M^{-1} for HP-β-CD and RM-β-CD, respectively. In acetate buffer (pH 4.5) gefitinib formed weak complexes with both CDs as indicated by the K_s of 71.4 and 102.5 M^{-1} for HP-β-CD and RM-β-CD, respectively. The phase solubility of gefitinib with HP-β-CD in distilled water in the presence of PVP or HPMC resulted in A_P type phase solubility diagrams indicating the formation of ternary complexes. DSC and XRD analyses indicate the formation of amorphous inclusion complexes in the solid state by these CDs by the freeze-drying method. The freeze-dried formulations showed substantial increases in the solubility and dissolution rate of gefitinib with both CDs compared to gefitinib alone. The addition of hydrophilic polymers to HP-β-CD provided further significant increases in the dissolution of gefitinib.

Acknowledgments

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Declaration of interest: The authors report no conflicts of interest.

References

1. Ranson M, Wardell S. (2004). Gefitinib, a novel, orally administered agent for the treatment of cancer. J Clin Phar Ther, 29:95–103.
2. Pao W, Miller VA, Kris MG. (2004). 'Targeting' the epidermal growth factor receptor tyrosine kinase with gefitinib (iressa) in non-small cell lung cancer (nsclc). Semin Cancer Biol, 14:33–40.
3. Bergman E, Forsell P, Persson EM, Knutson L, Dickinson P, Smith R, et al. (2007). Pharmacokinetics of gefitinib in humans: The influence of gastrointestinal factors. Int J Pharm, 341:134–42.
4. Siegel-Lakhai WS, Beijnen JH, Schellens JHM. (2005). Current knowledge and future directions of the selective epidermal growth factor receptor inhibitors erlotinib (tarceva) and gefitinib (iressa). Oncologist, 10:579–89.
5. Amidon GL, Lennernäs H, Shah VP, Crison JR. (1995). A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res, 12:413–20.
6. Swaisland HC, Smith RP, Laight A, Kerr DJ, Ranson M, Wilder-Smith CH, et al. (2005). Single-dose clinical pharmacokinetics studies of gefitinib. Clin Pharmacokinet, 44:1165–77.
7. Carrier RL, Miller LA, Ahmed I. (2007). The utility of cyclodextrins for enhancing oral bioavailability. J Control Release, 123:78–99.
8. Loftsson T, Brewster ME, Masson M. (2004). Role of cyclodextrins in improving oral drug delivery. Am J Drug Deliv, 2: 261–75.
9. Challa R, Ahuja A, Ali J, Khar RK. (2005). Cyclodextrins in drug delivery: An updated review. AAPS PharmSciTech, 6: E329–E357.
10. Loftsson T, Duchene D. (2007). Cyclodextrins and their pharmaceutical applications. Int J Pharm, 329:1–11.
11. Higuchi T, Connors KA. (1965). Phase solubility techniques. Adv Anal Chem Instrum, 4:117–212.
12. Takayama K, Nambu N, Nagai T. (1980). Pharmaceutical interactions in dosage forms and processing. XIX. Dissolution kinetics for coprecipitates of indomethacin with polyvinylpyrrolidone. Chem Pharm Bull, 28:3304–09.
13. Khan KA, Rhodes CT. (1972). Effect of compaction pressure on the dissolution efficiency of direct compression systems. Pharm Acta Helv, 47:594–607.
14. Liu X, Lin H-S, Thenmozhiyal JC, Chan SY, Ho PC. (2003). Inclusion of acitretin into cyclodextrins: Phase solubility, photostability, and physicochemical characterization. J Pharm. Sci, 92:2449–57.
15. Babu RJ, Pandit JK. (2004). Effect of cyclodextrins on the complexation and transdermal delivery of bupranolol through rat skin. Int J Pharm, 27:155–65.
16. Loftsson T, Gudmundsdóttir H, Sigurjónsdóttir JF, Sigurdsson HH, Sigfússon SD, Másson M, et al. (2001). Cyclodextrin solubilization of benzodiazepines: Formulation of midazolam nasal spray. Int J Pharm, 212:29–40.
17. Veiga F, Teixeira-Dias JJC, Kedzierewicz F, Sousa A, Maincent P. (1996). Inclusion complexation of tolbutamide with beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin. Int J Pharm, 129:63–71.
18. Botella SM, Martin MA, Del Castillo B, Menendez JC, Vazquez L, Lerner DA. (1996). Analytical applications of retinoid-cyclodextrin inclusion complexes. 1. Characterization of a retinal-beta-cyclodextrin complex. J Pharm Biomed Anal, 14:909–15.
19. Mura P, Adragna E, Rabasco AM, Moyano JR, Perez-Martinez JI, Arias MJ, et al. (1999). Effects of the host cavity size and the preparation method on the physicochemical properties of ibuproxam-cyclodextrin systems. Drug Dev Ind Pharm, 25:279–87.
20. Anzai K, Mizoguchi J, Yanagi T, Hirayama F, Arima H, Uekama K. (2007). Improvement of dissolution properties of a new Helicobacter pylori eradicating agent (TG44) by inclusion complexation with beta-cyclodextrin. Chem Pharm Bull (Tokyo), 55:1466–70.
21. Chowdary KPR, Srinivas SV. (2006). Influence of hydrophilic polymers on celecoxib complexation with hydroxypropyl beta-cyclodextrin. AAPS PharmSciTech, 7:E1–E6.
22. Mura P, Faucci MT, Bettinetti GP. (2001). The influence of polyvinylpyrrolidone on naproxen complexation with hydroxypropyl-beta-cyclodextrin. Eur J Pharm Sci, 13:187–94.