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Effect of HPMC concentration on β-cyclodextrin solubilization of norfloxacin

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ABSTRACT

The effect of hydroxypropyl methylcellulose (HPMC) concentration on β-cyclodextrin (β-CD) solubilization of norfloxacin was examined. The solubility and dissolution of norfloxacin/β-CD and norfloxacin/β-CD/HPMC inclusion complexes were studied. The presence of β-CD increased significantly the solubility and dissolution of norfloxacin. The addition of HPMC until 5% (w/w) improved the solubilization of norfloxacin but further addition above 5% (w/w), decreased norfloxacin solubilization. Fourier transformed Infra-red (FTIR) showed that norfloxacin was successfully included into β-CD. Differential scanning calorimetry (DSC) showed that the norfloxacin endothermic peak shifted to a lower temperature with reduced intensity indicating the formation of inclusion complex. The addition of HPMC reduced further the intensity of norfloxacin endothermic peak. Most of the sharp and intense peaks of norfloxacin disappeared with the addition of HPMC. In conclusion, the concentration of hydrophilic polymer used to enhance β-CD solubilization of poorly soluble drugs is very critical.

1. Introduction

Cyclodextrin inclusion complexation, which is the formation of host–guest inclusion complexes by weak intermolecular interaction, has been shown to be a promising technique in enhancing solubility and bioavailability of poorly water soluble drugs (Yang et al., 2011). There are different methods to prepare cyclodextrin inclusion complexes. These methods encompass co-precipitation (Bekerrs, Uijtendaal, Beijnen, Bult, & Underberg, 1997), kneading, lyophilization (Jarvinen, Jarvinen, Schwarting, & Stella, 1985), spray drying (Abosehmah-Albidy, York, Losowsky, & Chrystyn, 1985), freeze drying (Ammar, Ghorab, El-nahhas, Omar, & Ghorab, 1996) and supercritical fluid technology (Hanny & Hogarth, 1879).

Hydrophilic polymers have been reported to be able to enhance β-CD solubilization of poorly soluble drugs. Polyvinylpyrrolidone was reported to enhance cyclodextrin solubilization of triclosan through ternary drug-cyclodextrin-polymer complex formation (Loftsson & Masson, 2004; Jug, Kosalec, Maestrelli, & Mura, 2011). Saraf, Tripathi, Pandey, Yadav, and Saraf (2011) prepared inclusion complex of meloxicam/β-CD in which HPMC was added through physical mixing method.

HPMC is a water soluble polymer. There are various grades of HPMC available in the market. The effect of addition of HPMC on β-CD solubilization of poorly soluble drugs has not been thoroughly explored.

The purpose of the present study was to investigate the effect of HPMC on β-cyclodextrin solubilization of a poorly soluble drug, BCS Class IV agent, norfloxacin. In the present study, solvent evaporation method was used to prepare inclusion complex of norfloxacin/β-CD/HPMC.

The solubility and dissolution of norfloxacin/β-cyclodextrin and norfloxacin/β-cyclodextrin/HPMC were evaluated. In the present study, solvent evaporation method was used to prepare inclusion complex of norfloxacin/β-CD/HPMC. In addition, the solid complexes were characterized using differential scanning calorimeter (DSC), Fourier transformed Infra-red (FTIR) and X-ray powder diffraction (XRD).

2. Materials and methods

2.1. Materials

Norfloxacin was purchased from Boom Buying PVT LTD (Delhi, India). HPMC was obtained from ISP Technologies Inc. (Wayne, NJ). β-CD was provided by Roquette (Lestrem, France). All other materials were of analytical reagent grade and used as received.

2.2. Methods

2.2.1. Phase solubility study

Phase solubility study was performed according to the method of Higuchi and Connors (1961). An excess amount of norfloxacin

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was added into 50 mL of distilled water containing various concentrations of βCD (2–20 mM). HPMC of 2.5 and 5% (w/v) was added to the mixture of norfloxacin/β-CD. The flasks were shaken continuously at 30 °C for 3 days to reach equilibrium. Samples of 3 mL were withdrawn and filtered through a 0.45 μm nylon membrane filter. 100 μL of filtrate was diluted appropriately and assayed spectrophotometrically (U-2000 Spectrophotometer, Hitachi, Tokyo, Japan) at 278 nm. Each measurement was run three times.

The stability constant was calculated from the phase solubility diagrams using the following equation,

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{slope})}$$

The slope was obtained from the plot of norfloxacin concentration against β-CD concentration with and without 2.5 and 5% (w/v) of HPMC. S_0 was the equilibrium solubility of norfloxacin in water.

2.2.2. Preparation of norfloxacin/β-cyclodextrin inclusion complex

Norfloxacin/β-CD inclusion complex was prepared at weight ratios of 1:1, 1:2 and 1:4. Norfloxacin was dissolved in 25 mL of acetone, while β-CD was dissolved in 50 mL of distilled water. The two solutions were mixed together and stirred for 1 h. Acetone was evaporated off by heating at 50 °C under constant stirring. Water was then removed under reduced pressure using rotary evaporator. The mixture was placed overnight (24 h) in an oven at 50 °C to remove residual solvent. The inclusion complex was ground using mortar and pestle and sieved through mesh #65 (0.211 mm).

2.2.3. Preparation of norfloxacin/β-cyclodextrin/HPMC complex

Norfloxacin/β-CD at ratio of 1:1 was prepared. HPMC at concentrations of 2.5, 5.0, 7.5 and 10.0% (w/w) at dry weight of inclusion complex, were added to the mixture. The mixture was stirred for an hour. Acetone was then evaporated off by heating at 50 °C under continuous stirring. Water from the mixture was removed under reduced pressure using rotary evaporator. The mixture was placed in an oven at 50 °C overnight (24 h) to remove residual solvent. The dried complex was ground using mortar and pestle and sieved through mesh #65 (0.211 mm).

2.2.4. Scanning electron microscopy (SEM)

The surface morphology of samples was examined using a LEO 1530 Field Emission Scanning Microscope (FESEM; Leosupra 50VP, Carl Zeiss, Oberkochen, Germany) at 2 keV. The samples were sputtered with a thin layer of gold to improve the electrical conductivity prior to imaging.

2.2.5. Solubility studies

An excess amount of solid complexes were dispersed in 50 mL of distilled water. The flasks were vortex-mixed for 3 min and agitated at 120 rounds per minute in a water bath maintained at 30 °C for 72 h. Samples of 3 mL were withdrawn and filtered through a 0.45 μm nylon membrane filter. 100 μL of filtrate was diluted appropriately and measured spectrophotometrically (Hitachi U-2000 Spectrophotometer; Hitachi Ltd, Tokyo Japan) at 278 nm. Each measurement was repeated three times.

2.2.6. In vitro dissolution studies

In vitro dissolution studies were performed for both norfloxacin and the complexes using USP dissolution tester (PTWS 3CE, Pharmatest, Germany) apparatus II paddle method (USP XXXII, 2009). The dissolution medium was comprised of 900 mL of distilled water maintained at 37.0 ± 0.5 °C with a paddle rotation speed of 100 rpm. The amount of powder equivalent to 20 mg of drug was accurately weighed into each vessel. Samples of 3 mL were withdrawn automatically at preset time intervals of 10, 20, 30, 40, 50 and 60 min filtered through 0.45 μL nylon membrane filter. The drug concentration in the sample was analyzed using UV spectrophotometer (Hitachi U-2000 Spectrophotometer; Hitachi Ltd, Tokyo Japan) at 278 nm. The $t_{50\%}$ value (time for 50% of drug released) was estimated from the individual percentage drug release against time curve as a time taken for 50% of drug released and the mean $t_{50\%}$ value calculated.

2.2.7. Drug content analysis

Norfloxacin/β-CD and norfloxacin/β-CD/HPMC complexes (20 mg) were placed in 50 mL volumetric flask. 20 mL of 0.05 M sodium hydroxide (NaOH) solution was added and sonicated for 10 min. The solution was cooled to room temperature and topped up to volume with 0.05 M NaOH solution. The sample was diluted appropriately with 0.05 M NaOH and measured spectrophotometrically (U2000 Spectrophotometer, Hitachi, Japan) at 278 nm. Each measurement was run three times.

2.2.8. Differential scanning calorimetry (DSC)

Differential scanning calorimetry measurement was performed using differential scanning calorimeter (DSC, Perkin Elmer, Pyris 6 System, USA). Sample weight of 3–10 mg was put in crimped aluminum pan and heated over a temperature range of 0–350 °C at a constant rate of 10 °C/min under nitrogen flow of 20 mL/min. An empty aluminum pan was used as a reference.

2.2.9. Fourier transform infra-red spectroscopy (FTIR)

1 mg of sample and 100 mg of potassium bromide (KBr) were mixed and pressed into a disk using a hydraulic pressure at 15 ton. The sample was scanned over a spectral region from 400 to 4000 cm^{-1} (Nexus FTIR, J Thermo Nicolet, USA).

2.2.10. Powder X-ray diffraction analysis (XRD)

The physical state of norfloxacin in the complex was evaluated using X-ray diffractometer (Siemens D 5000, Germany). The X-ray source was Kα radiation from a copper target with graphite monochromater. The X-ray tube was operated at a voltage of 40 kV and a current of 30 mA. The scanning rate was 6°/min over a 2θ range of 5–80° with a chart speed of 5°/min at increment of 0.05°.

2.2.11. Statistical analysis

The results were presented in mean ± SD. The solubility data was analyzed using one-way analysis of variance (ANOVA). When there was a statistically significant difference, post hoc Tukey-HSD test was carried out. A significant level was set at $p < 0.05$.

3. Results and discussion

3.1. Phase solubility study

Phase solubility study was performed to investigate the solubility of norfloxacin in β-CD with and without the presence of HPMC. From Fig. 1, it can be seen that solubility of norfloxacin increased proportionally with an increase in the concentration of β-CD. With the addition of HPMC in β-CD, the solubility of norfloxacin was further increased. It can be observed from Fig. 2 that norfloxacin solubility was comparatively higher in 5.0% (w/v) than 2.5% HPMC in β-CD.

The stability constant (*Ks*) value was found to increase from 103.49 M^{-1} for β-CD to 253.34 M^{-1} and 307.49 M^{-1} as a result of addition of 2.5% (w/v) and 5% (w/v) HPMC. These values indicated the formation of a comparatively more stable complex of norfloxacin/β-CD/HPMC than norfloxacin/β-CD. Addition of water soluble polymers to such systems increases stability constant of the drug/CD complex leading to more enhanced drug solubilization. It was reported that stability constant (*Ks*) value between 50 and

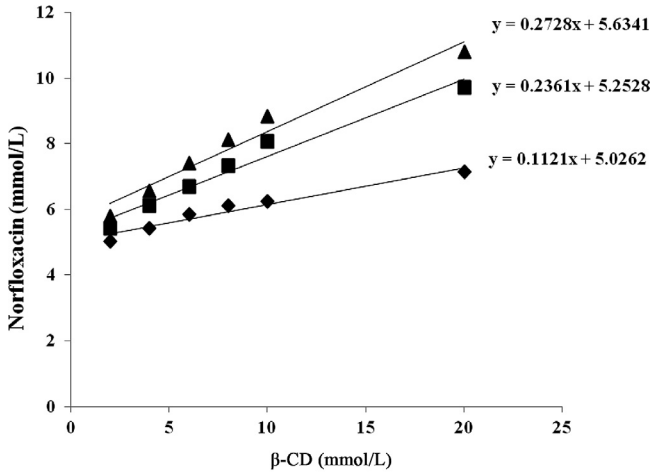

Fig. 1. Phase-solubility diagram of norfloxacin in aqueous solution of β-CD without HPMC (♦); with 2.5% (w/v) HPMC (■) and 5.0% (w/v) of HPMC (♦). Mean ± SD, $N = 3$.

5000 M^{-1} was considered as most suitable for the improvement of solubility and stability of poorly soluble drugs (Patel & Patel, 2007).

3.2. Scanning electron microscopy (SEM)

Fig. 2 shows the SEM micrographs of norfloxacin, HPMC, β-CD, norfloxacin/β-CD and norfloxacin/β-CD/HPMC inclusion complexes. Norfloxacin appears to be a compact solid with rather smooth surface. HPMC appears to be thin, slightly crumpled, elongated solid. β-CD appears to be thick with non-smooth surface. The compact solid appearance of norfloxacin could not be observed in norfloxacin/β-CD (1:1) inclusion complex. For inclusion complex of norfloxacin/β-CD/HPMC, it appeared to look like HPMC layered on the surface of norfloxacin/β-CD indicating the formation of ternary complexes. For HPMC of 5% (w/w), the presence of HPMC layered on the surface of norfloxacin/β-CD was more obvious.

3.3. Solubility study

The solubility data of norfloxacin are presented in Table 1. Norfloxacin solubility was significantly increased ($p < 0.05$) from 0.39 mg/mL to 4.23 mg/mL with the addition of β-CD (1:1). A comparatively higher solubility value of 5.35 mg/mL was observed with the use of a higher amount of β-CD (1:2). However, there was no statistically significant difference in the solubility of norfloxacin with further increase in the amount of β-CD from 1:2 to 1:4 ($p > 0.05$). This result suggested that norfloxacin and β-CD at a ratio of 1:2 was optimum.

Table 1
Solubility data of norfloxacin in β-CD and β-CD/HPMC aqueous solution. Mean ± SD, $N = 3$.

Norfloxacin: β-CD (w/w)	Solubility (mg/mL)
1:0	0.39 ± 0.01
1:1	4.23 ± 0.03
1:2	5.35 ± 0.05
1:4	5.36 ± 0.11
1:1 (2.5%HPMC)	4.70 ± 0.05
1:1 (5.0%HPMC)	6.92 ± 0.08
1:1 (7.5%HPMC)	6.53 ± 0.16
1:1 (10.0%HPMC)	6.06 ± 0.05

Norfloxacin/βCD at a ratio of 1:1 was selected for further study to examine the effect of HPMC on solubility of norfloxacin. This is because at this ratio, the solubility of norfloxacin has been drastically increased. The use of a higher amount of β-CD increased only slightly the norfloxacin solubility although the increase was found to be significant. As the dose of norfloxacin used in treatment is 400 mg, the total solid is 800 mg at ratio of 1:1. When the ratio is increased to 1:2, the total solid needed to produce equivalent amount of drug will be 1200 mg. The weight will be further compounded with the presence of HPMC.

It was noted that the solubility of norfloxacin was significantly increased ($p < 0.05$) with an addition of 2.5% (w/w) of HPMC. A further increase to 5% (w/w) of HPMC increased further the solubility of norfloxacin ($p < 0.05$). However, when the percentage of HPMC was further increased to 7.5% (w/w), there was a slight decrease in the solubility of norfloxacin. At a higher amount of HPMC at 10% (w/w), the solubility of norfloxacin/β-CD was further decreased. This showed that 5% of HPMC was optimal in improving β-CD solubilization of norfloxacin. Similar findings were reported by Faucci and Mura (2001) and Loftsson and Masson (2004). Mixtures of polymers and CDs were more effective to solubilize naproxen than either polymers or CDs when used alone.

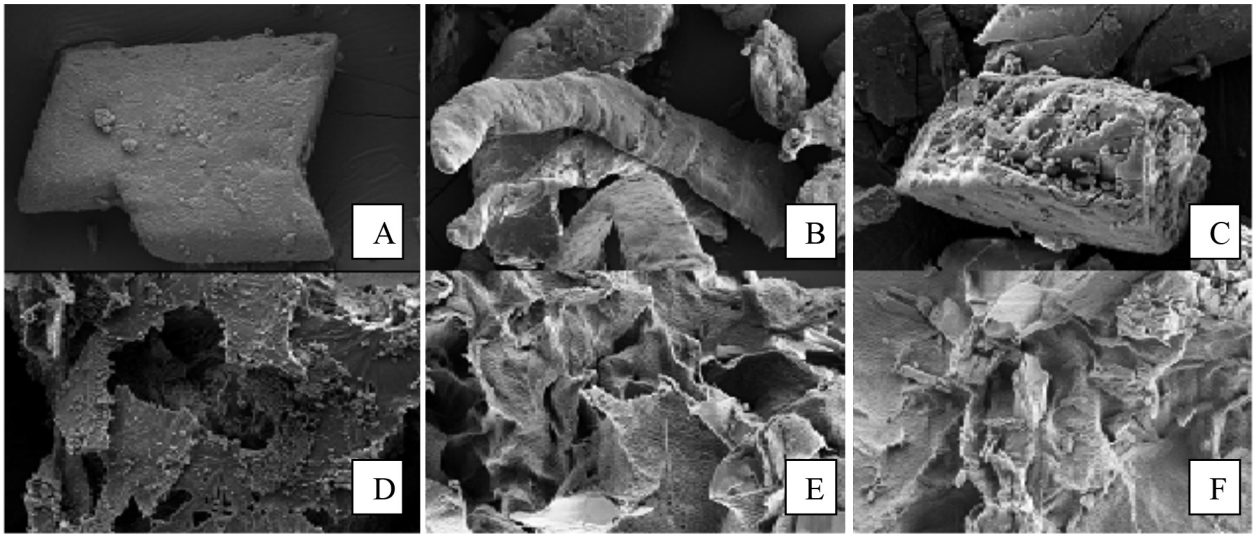

Fig. 2. (A) Norfloxacin; (B) HPMC; (C) β-CD; (D) Norfloxacin/β-CD (1:1); (E) Norfloxacin/β-CD/HPMC complex (1:1:2.5%) and (F) Norfloxacin/β-CD/HPMC complex (1:1:5.0%) (1000X magnification).

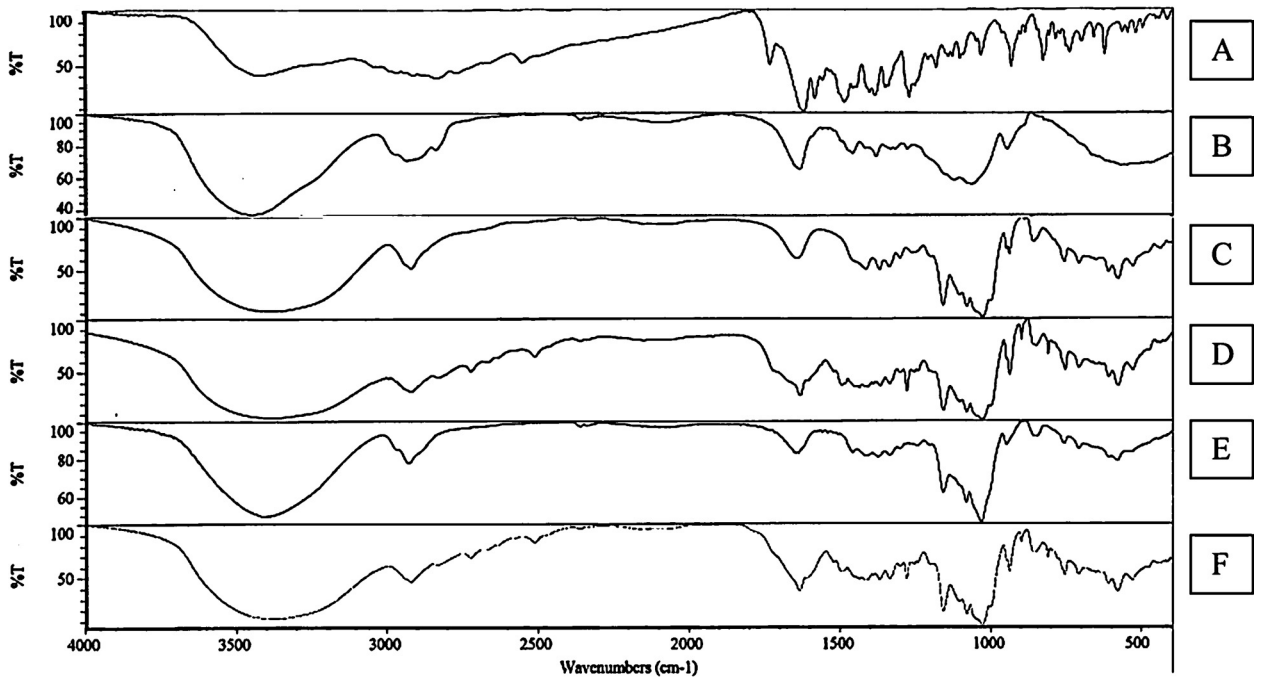

Fig. 3. FTIR spectral of (A) Norfloxacin; (B) HPMC; (C) β-CD; (D) Norfloxacin/β-CD inclusion complex (1:1); (E) Norfloxacin/β-CD/HPMC complex (1:1:2.5%) and (F) Norfloxacin/β-CD complex/HPMC (1:1:5%).

This result could be attributed to an overall improvement in solubility of norfloxacin when both HPMC and β-CD were used in the formation of solid complexes. The observed solubility enhancement is both due to enhanced complexation efficacy and increased solubility of both CD and β-CD complexes upon ternary complex formation in the aqueous complexation media. Solubility of β-CD is relatively low (1.85 g/100 mL) which is mainly due to formation of intermolecular hydrogen bonds between C2, C3 hydroxyl group in β-CD molecule (Qian, Guan, & Xiao, 2008). Valero, Perez-Revuelta, and Rodrfguez (2003) reported a ternary system consisting of naproxen, β-CD and PVP. The polymer partly or totally coated the naproxen/β-CD inclusion complex interacting with both naproxen and β-CD through hydrogen bonds, showing more affinity for the inclusion complex than the free drug.

The increase in β-CD solubilization of norfloxacin by HPMC could be due to the interaction of hydroxypropyl methyl group of HPMC and hydroxyl group of β-CD, which might interrupt the intermolecular hydrogen bonding between C2 and C3.

CDs are generally unable to form inclusion complexes with polymers with their effective diameter because the diameter of the hydrated polymer chain is greater than that of the cavity of CD. The effective diameter of β-CD is between 0.60 and 0.65 nm. In general, some water soluble polymers such as methylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone have effective diameter much greater than the effective diameter of β-CD. Furthermore, these polymers are hydrophilic in nature which is unable to form inclusion complex with the lipophilic cavity of β-CD. Therefore, these polymers are not able to form inclusion complexes with β-CD (Szejtli, 1988). This also provides explanation on the decrease in solubilization of norfloxacin when HPMC was increased to 7.5% (w/w).

3.4. Drug content analysis

The content of norfloxacin was within 97–100% for all complexes, showing that the drug was distributed uniformly.

3.5. FTIR

FTIR is a useful technique to study the occurrence of inclusion (Szente, 1996). Fig. 3 shows the FTIR spectra of norfloxacin, β-CD, and inclusion complexes. Norfloxacin showed a strong absorption peak at 1720 cm^{-1}, corresponded to COOH peak. However, there were obvious changes in the spectrum for the inclusion complex of norfloxacin/β-CD showing disappearance of COOH, suggesting

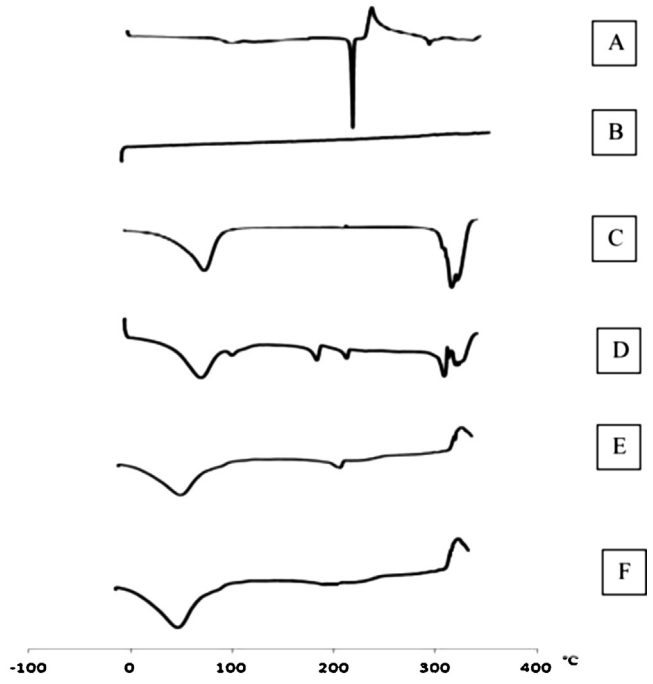

Fig. 4. Thermograms of (A) Norfloxacin; (B) HPMC; (C) β-CD; (D) Norfloxacin/β-CD inclusion complex (1:1); and (E) Norfloxacin/β-CD/HPMC complex (1:1:2.5%) and (F) Norfloxacin/β-CD complex/HPMC (1:1:5.0%).

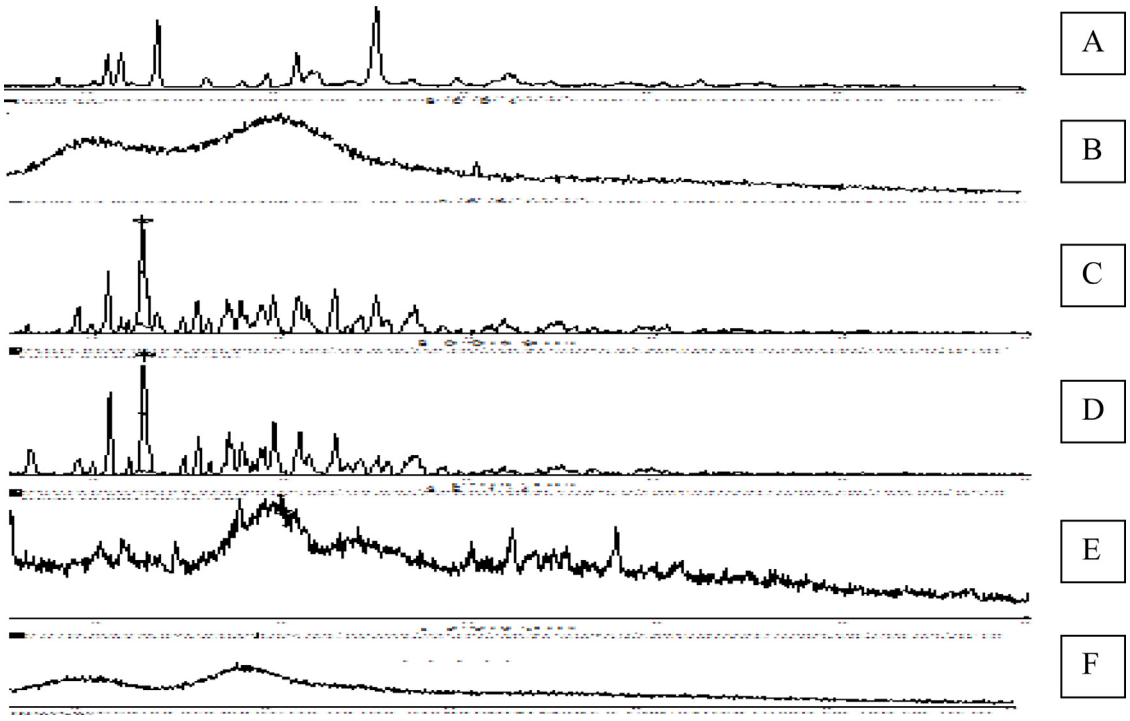

Fig. 5. Powder X-ray diffraction pattern of (A) Norfloxacin; (B) HPMC; (C) β-CD; (D) Norfloxacin/β-CD inclusion complex (1:1); (E) Norfloxacin/β-CD/HPMC complex (1:1:2.5%) and (F) Norfloxacin/β-CD complex/HPMC (1:1:5%).

this functional group is included within the apolar cavity of β-CD. Similarly, the complex of norfloxacin/β-CD/HPMC showed the absence of absorption band corresponding to COOH stretching vibration, suggesting chemical interaction between norfloxacin and β-CD/HPMC and hence the formation of inclusion complex.

3.6. DSC

The thermograms of norfloxacin and the complexes are shown in Fig. 4. Norfloxacin showed a very sharp endothermic peak at 220 °C, which corresponded to the melting temperature of norfloxacin. β-CD showed two endothermic peaks, which corresponded to loss of water molecule at around 80 °C and melting temperature at above 300 °C. Inclusion complex of norfloxacin/β-CD (1:1) showed an endothermic peak which shifted to a lower temperature with reduced intensity suggesting the formation of inclusion complex. In the case of norfloxacin/β-CD/HPMC (1:1:2.5%), the endothermic peak which corresponded to the melting point of norfloxacin is very negligible, suggesting the disappearance and reduction in intensity of endothermic peak.

3.7. XRD study

As shown in Fig. 5, norfloxacin and β-CD appeared in crystalline form but β-CD showed less crystalline peaks whereas HPMC was amorphous. The powder X-ray diffraction patterns of the β-CD

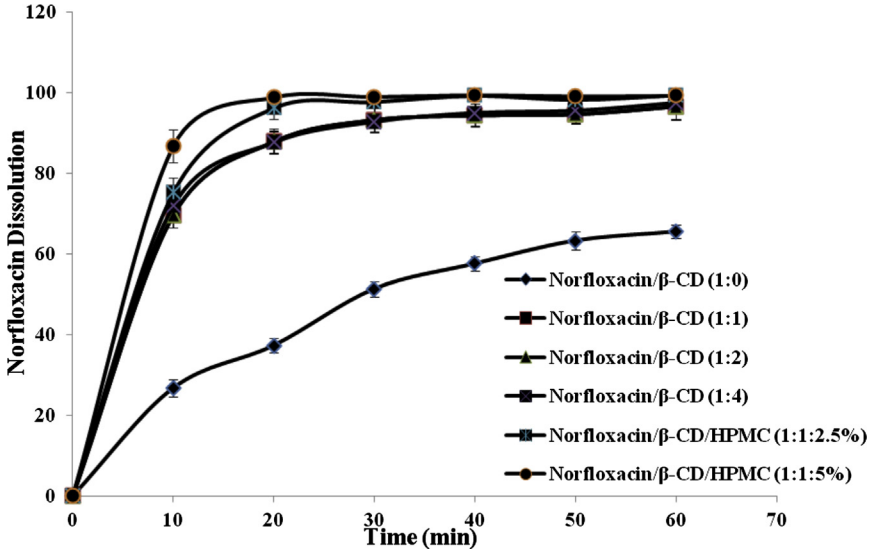

Fig. 6. Mean dissolution profiles of norfloxacin, norfloxacin/HPMC, norfloxacin/β-CD and norfloxacin/β-CD/HPMC complexes. Mean ± SD, $N = 3$.

Table 2
The $t_{50\%}$ values of norfloxacin and solid complexes. Mean ± SD, $N = 6$.

Norfloxacin/β-CD/HPMC	t_{50}% (min)		
1.0:0.0:0.0%	28.67 ± 1.75	–	–
1.0:1.0:0.0%	–	7.08 ± 0.49	–
1.0:2.0:0.0%		6.87 ± 0.41	
1.0:4.0:0.0%		6.83 ± 0.47	
1.0:1.0:2.5%	–	–	6.50 ± 0.45
1.0:1.0:5.0%	–	–	6.00 ± 0.32

revealed some crystalline peaks suggesting it is not an amorphous compound. Inclusion complex of norfloxacin/β-CD also showed several crystalline peaks identical to its parent product but with reduced intensity. This result indicated that β-CD was not able to convert norfloxacin to amorphous state. In contrast, norfloxacin/β-CD/HPMC complex showed a halo pattern indicating the formation of amorphous norfloxacin. Compared to 2.5% HPMC, 5% HPMC was noted to be more amorphous, with no crystalline peak as shown in Fig. 5. The results are consistent with the findings of DSC on the complexes.

3.8. *In vitro dissolution study*

Fig. 6 shows the dissolution profiles of norfloxacin, inclusion complexes and inclusion complexes with addition of HPMC at 2.5 and 5% (w/w). As expected, norfloxacin exhibited the slowest dissolution rate compared to other formulations, which is mainly due to its low solubility in water. Norfloxacin was released about 60% after an hour.

The complexation with β-CD improved the dissolution rate of norfloxacin significantly when compared with the dissolution of norfloxacin. An addition of HPMC did not appear to increase drastically the release of norfloxacin.

The $t_{50\%}$ (time for 50% of drug released) results are shown in Table 2. Norfloxacin exhibited the longest $t_{50\%}$ when compared with norfloxacin/β-CD inclusion complex and ternary complex of norfloxacin/β-CD/HPMC. The addition of HPMC increased only slightly the dissolution rate of norfloxacin.

4. Conclusions

In can be concluded that inclusion complexation with β-CD increased significantly both solubility and dissolution of poorly soluble norfloxacin. The addition of HPMC further increased norfloxacin solubility but until 5.0% (w/w). Further addition of HPMC adversely reduced norfloxacin solubility. Hence, the concentration of hydrophilic polymer used is very critical. Inappropriate concentration of hydrophilic polymer can adversely affect β-CD solubilization of poorly soluble drugs.

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References

Abosehmah-Albidy, A. Z., York, P. W. V., Losowsky, M. S., & Chrystyn, H. (1997). Improved bioavailability and clinical response in patients with chronic liver disease following the administration of a spironolactone: β-Cyclodextrin complex. *British Journal of Clinical Pharmacology*, *44*, 35–39.

Ammar, H. O., Ghorab, M., El-nahhas, S. A., Omar, S. M., & Ghorab, M. M. (1996). Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation, part 5. Theophylline. *Pharmazie*, *54*, 42–46.

Bekerrs, O., Uijtendaal, E. V., Beijnen, J. H., Bult, A., & Underberg, W. J. M. (1991). Cyclodextrins in the pharmaceutical field. *Drug Development and Industrial Pharmacy*, *17*, 1503–1549.

Faucci, M. T., & Mura, P. (2001). Effect of water-soluble polymers on naproxen complexation with natural and chemically modified β-cyclodextrins. *Drug Development and Industrial Pharmacy*, *27*, 909–917.

Hanny, J. B., & Hogarth, J. (1879). On the solubility of solids in gases. *Royal Society (London)*, *29*, 324.

Higuchi, T., & Connors, K. A. (1961). Phase-solubility techniques. *Advances in Analytical Chemistry and Instrumentation*, *4*, 117–212.

Jarvinen, T., Jarvinen, K., Schwarting, N., & Stella, V. J. (1985). β- Cyclodextrin derivatives, SBE4-β-CD and HP-β-CD, increase the oral bioavailability of cinnarizine in beagle dogs. *Journal of Pharmaceutical Sciences*, *84*, 295–299.

Jug, M., Kosalec, I., Maestrelli, F., & Mura, P. (2011). Analysis of triclosan inclusion complexes with β-cyclodextrin and its water-soluble polymeric derivative. *Journal of Pharmaceutical and Biomedical Analysis*, *54*, 1030–1039.

Loftsson, T., & Masson, M. (2004). The effects of water soluble polymers on cyclodextrins and cyclodextrin solubilization of drugs. *Journal of Drug Development and Science Technology*, *14*, 35–43.

Patel, R. P., & Patel, M. M. (2007). Preparation and evaluation of inclusion complex of lipid lowering drug lovastatin with β-cyclodextrin. *Dhaka University Journal of Pharmaceutical Sciences*, *6*(1), 25–36.

Qian, L., Guan, Y., & Xiao, H. (2008). Preparation and characterization of inclusion complexes of a cationic β-cyclodextrin polymer with butylparaben or triclosan. *International Journal of Pharmaceutics*, *357*, 244–251.

Saraf, S. A., Tripathi, G. T., Pandey, M., Yadav, P., & Saraf, S. K. (2011). Development of meloxicam formulations utilizing ternary complexation for solubility enhancement. *Pakistan Journal of Pharmaceutical Sciences*, *24*(4), 533–538.

Szente, L. (1996). Cyclodextrins. In J. Szejtli, & T. Osa (Eds.), *Comprehensive supramolecular chemistry* (pp. 253–278). Oxford, UK: Pergamon.

Szejtli, J. (1988). *Cyclodextrin technology*. Drodrecht: Kluwer Academic Publisher.

Valero, M., Perez-Revuelta, B. I., & Rodrfguez, L. J. (2003). Effect of PVP K-25 on the formation of naproxen:β-cyclodextrin complex. *International Journal of Pharmaceutics*, *253*(1/2), 97–110.

Yang, L. J., Chen, W., Ma, S.-X., Gao, Y.-T., Huang, R., Yan, S. J., et al. (2011). Host–guest system of taxifolin and native cyclodextrin or its derivative: Preparation, characterization, inclusion mode, and solubilization. *Carbohydrate Polymers*, *85*, 629–637.