



Enhancement of Dissolution of Fenofibrate Using Complexation with Hydroxy Propyl β -Cyclodextrin

Hidroksi Propil β -Siklodekstrin ile Kompleksasyon Kullanılarak Fenofibratın Çözünmesinin Arttırılması

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ABSTRACT

Objectives: The aim of the present study was to enhance the dissolution rate of fenofibrate using complexation with hydroxy propyl β -cyclodextrin (HP β CD).

Materials and Methods: The phase solubility behavior of fenofibrate was studied in various concentrations of (HP β CD) aq. solution at 37°C. The solubility of fenofibrate increased with an increase in the amount of HP β CD aq. solution. Gibbs free energy (ΔG°)_{ir} values were all negative. Complexes of fenofibrate with HP β CD were prepared in 1:1 ratio by kneading and coprecipitation. These complexes were evaluated by dissolution studies, fourier transform infrared (FTIR) spectroscopy, and differential scanning calorimetry (DSC) studies.

Results: The complexation of fenofibrate with HP β CD exhibited an enhanced dissolution rate. The mean dissolution time of fenofibrate decreased significantly upon complexation. FTIR studies showed the formation of intermolecular hydrogen bonding between fenofibrate and HP β CD. DSC studies indicated a loss in crystalline state of fenofibrate in complexes.

Conclusion: Complexation with HP β CD can be used as a useful tool for the enhancement of dissolution of fenofibrate.

Key words: Fenofibrate, hydroxy propyl β -cyclodextrin, solubility, Gibbs free energy, dissolution rate

ÖZ

Amaç: Bu çalışmanın amacı, hidroksi propil β -siklodekstrin (HP β CD) ile kompleksasyon kullanarak fenofibratın çözünme hızını arttırmaktır.

Gereç ve Yöntemler: Fenofibratın faz çözünürlük davranışları (HP β CD) çeşitli konsantrasyonlardaki sulu çözeltisinde, 37°C'de çalışıldı. Fenofibratın çözünürlüğü, artan miktarda HP β CD'nin sulu çözeltisi ile arttı. Gibbs serbest enerji (ΔG°)_{ir} değerlerinin hepsi negatifti. HP β CD ile fenofibrat kompleksleri, 1:1 oranında yoğurma ve kopresipitasyon ile hazırlandı. Bu kompleksler, çözünme çalışmaları, fourier dönüşümü kızılötesi spektroskopisi (FTIR) ve diferansiyel tarama kalorimetrisi (DSC) çalışmaları ile değerlendirildi.

Bulgular: Fenofibratın HP β CD ile kompleksasyonu, gelişmiş bir çözünme hızı sergiledi. Fenofibratın ortalama çözünme süresi, kompleksasyon üzerine önemli ölçüde azaldı. FTIR çalışmaları fenofibrat ve HP β CD arasında moleküller arası hidrojen bağlanmasının oluşumunu göstermiştir. DSC çalışmaları komplekslerde kristalin fenofibrat durumunda bir kayıp olduğunu gösterdi.

Sonuç: HP β CD ile kompleksasyon, fenofibratın çözünmesinin arttırılması için yararlı bir araç olarak kullanılabilir.

Anahtar kelimeler: Fenofibrat, hidroksi propil β -siklodekstrin, çözünürlük, Gibbs serbest enerjisi, çözünme hızı

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INTRODUCTION

Fenofibrate, propan-2-yl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropanoate, is a fibric acid derivative useful as an antilipidemic agent. Fenofibrate is a hypolipidemic drug that reduces the levels of lipids (fats) in the blood. It is a white crystalline powder, practically insoluble in water (log p=5.24).¹ Its low water solubility and poor dissolution rate cause problems in formulation development and restrict its therapeutic application by influencing the rate of absorption and the onset of action.

Consequently, its bioavailability is incomplete, irregular, and often varies from one person to another. As a result, commercially available doses are of higher strength and require repeated dosing. From an economic point of view, this low bioavailability of drug leads to wastage of more amounts of drug after oral administration, increasing the cost of medication. Therefore, it is very important to find appropriate formulation approaches to enhance the aqueous solubility, dissolution rate, and thus the bioavailability of poorly soluble drugs. Nowadays, many approaches are used to enhance the solubility and dissolution rate of poorly soluble drugs by the use of pharmaceutical technology.² Physical modification often aims to increase the surface area, solubility, and/or wettability of the powder. Other approaches include cosolvency using various solvent blends, cyclodextrin complexation,³ use of surfactants,⁴ salt forms,⁵ prodrugs,⁶ and alteration of crystal properties.^{7,8}

A number of different microorganisms and plants produce certain enzymes called cyclodextrin glucosyltransferases, which degrade starch to cyclic products called cyclodextrins. These cyclodextrins are cyclic oligosaccharides involving (α-1,4)-associated α-D-glucopyranose units and contain a genuinely lipophilic cavity and a hydrophilic external surface. They are shaped like truncated cones rather than perfect cylinders. In light of such qualities, cyclodextrins are able to form inclusion complexes both in solid state and in solution state, in which every guest entity is surrounded by the hydrophobic environment of the cyclodextrin cavity. Upon inclusion, the water solubility of the guest can increase as well as its bioavailability.^{9,10} This inclusion complex formation leads to alteration of the physicochemical and biological properties of the guest molecules and may eventually have considerable pharmaceutical potential.^{11,12}

The naturally occurring α-, β-, and γ-cyclodextrin consist of six, seven, and eight glucopyranose units, respectively. Natural cyclodextrins like β-cyclodextrin have limited aqueous solubility and the complexes formed from the interaction of lipophilic/hydrophobic drugs with these cyclodextrins may be of limited solubility. This may result in precipitation of solid cyclodextrin complexes from water and other aqueous systems. Cyclodextrin derivatives of pharmaceutical interest include the derivatives of these naturally occurring β- and γ-cyclodextrins. Out of these cyclodextrin derivatives, hydroxy propyl β-cyclodextrin (HPβCD) appears the most useful as a pharmaceutical complexing agent because of its complexing ability, low cost, and other properties. The approach of

cyclodextrin complexation can be used to increase the water solubility and dissolution rate of poorly soluble drugs and to solve bioavailability problems.

As fenofibrate dissolves very slightly in water, the present study was undertaken to overcome the limitations existing in available fenofibrate products so as to improve the dissolution profile, absorption characteristics, and bioavailability and to reduce the dose required for administration to attain a desired effect.

The study also aimed to develop a method for preparation of an inclusion complex of fenofibrate with HPβCD that is efficient and economical, simple, and less time consuming than other methods.

Thus, the present study was performed to enhance the solubility and dissolution rate of fenofibrate using complexation with HPβCD in order to attain a therapeutic effect. The possible interactions between fenofibrate and HPβCD in both solid state and liquid states were investigated. The solid state interaction was investigated by fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) studies. The interaction in solution was studied by phase solubility analysis and dissolution experiments.

MATERIALS AND METHODS

Materials

A gift sample of fenofibrate was received from Shreya Life Sciences, (Aurangabad, India). HPβCD was obtained from Wockhardt Pharmaceuticals (Aurangabad, India). All other solvents and ingredients used were of analytical grade.^{13,14}

Methods

Phase solubility studies

Phase solubility studies were performed in triplicate according to the method reported by Higuchi and Connors.¹⁵ An excess of drug was added to 5-mL portions of distilled water in vials each containing a variable amount of HPβCD (2 mM to 10 mM). All the above solutions were subjected to sonication for 30 min and then allowed to stand at room temperature (~25°C) for 48 h without disturbance to attain saturation equilibrium. These saturated systems were carefully filtered through Whatman filter paper (no. 41) and were analyzed spectrophotometrically at 287 nm after appropriate dilutions on a ultraviolet (UV)-visible spectrophotometer.

The solubility of fenofibrate in every HPβCD solution was calculated and a phase solubility diagram was drawn between solubility of fenofibrate and different concentrations of HPβCD. The apparent stability constant (Kc) was calculated by using the formula¹⁵;

$$\text{Stability constant (Kc)} = \frac{\text{Slope}}{\text{So (1-slope)}} \dots\dots\dots 1$$

where So=aqueous solubility of fenofibrate.

The Gibbs free energy of transfer (ΔG°_{tr}) of fenofibrate from pure water to the aqueous solution of carrier was calculated as¹⁴;

$$\Delta G_{tr} = 2.303 RT \log \text{So} / \text{Ss}, \dots\dots\dots 2$$

where S_o/S_s is the ratio of molar solubility of fenofibrate in aqueous solution of HP β CD to that of the same medium without HP β CD.

Preparation of solid binary systems

Preparation of physical mixture of fenofibrate with HP β CD

The physical mixture of fenofibrate with HP β CD containing molar weight ratio 1:1 (fenofibrate:HP β CD) was prepared, followed by passing through a sieve (no. 72) with minimum abrasion.

Preparation of inclusion complex by kneading method¹⁵

Stoichiometric quantities (1:1) of fenofibrate:HP β CD were accurately weighed. HP β CD was added to the mortar, and a small amount of ethanol:water (1:1 v/v) was added while triturating to get a slurry-like consistency. Then slowly the drug was incorporated into the slurry, and trituration was continued for a further 45 min. The slurry was then dried at 50°C for 24 h, pulverized, passed through a no. 72 sieve, and stored in desiccators until further use.

Preparation of inclusion complex by coprecipitation

Fenofibrate and HP β CD in 1:1 molar ratio were accurately weighed. Saturated cyclodextrin solution was prepared with HP β CD and water. Then fenofibrate solution in methanol was added slowly and a suspension was formed. The suspension was stirred at 40°C for 30 min and the stirring was continued at room temperature (25°C) for 30 min. The obtained masses were filtered through Whatman filter paper no. 41 and dried at 50°C in an oven for 24 h. The dried complexes were pulverized and passed through a no. 72 sieve and stored in desiccators until further use.¹⁶

The yield for HP β CD complex was not significant. Therefore, we used the following method for coprecipitation.

Fenofibrate and HP β CD in 1:1 molar ratio were accurately weighed. Cyclodextrin solution was prepared with HP β CD and water. Then fenofibrate solution in methanol was added slowly to the above solution and a suspension was formed. The suspension was stirred at 40°C for 30 min and kept stirring at room temperature for 12 h. The obtained masses were refrigerated for 24 h. Then these masses were filtered through Whatman filter paper no. 41 and dried at 50°C in an oven for 24 h. The dried complexes were pulverized and passed through a no. 72 sieve and stored in desiccators until further use.¹⁷

Dissolution studies

As fenofibrate is a lipophilic compound and practically insoluble in water, dissolution study of fenofibrate dosage forms necessitates modifications in the dissolution medium. Sodium lauryl sulfate (SLS) of concentration 20 mM and above provides sink conditions.^{18,19}

Dissolution studies of fenofibrate, physical mixture, kneaded product, and coprecipitated product were performed using the U.S. Pharmacopeia (USP) model digital tablet dissolution test apparatus II (Electrolab, Mumbai) at paddle rotation speed of 75 rpm in 900 mL of 20 mM SLS at 37.0 \pm 0.5°C.

The physical mixture equivalent to 145 mg of fenofibrate was weighed using a digital balance (Make Eagle, India) and added to dissolution medium. Then 5-mL samples were withdrawn at predetermined intervals and replaced with fresh dissolution medium and suitably diluted. Diluted samples were then assayed for fenofibrate content by measuring the absorbance at 287 nm using a UV-visible spectrophotometer (Jasco model V630, Japan). The dissolution studies were either performed until all the solids were completely dissolved or stopped at 2 h if the duration of dissolution was longer. Studies were performed in triplicate (n=3). Mean values of cumulative drug release were calculated for plotting the release curve.

Fourier transform infrared spectroscopy

FTIR spectra were obtained using an FT/IR-4100 spectrophotometer (Jasco, Japan). The samples (fenofibrate, physical mixture, and drug:cyclodextrin complexes) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (sample: KBr) ratio, respectively. Forty scans were obtained from 4000 to 400 cm⁻¹.

Differential scanning calorimetry studies

The DSC thermograms were obtained on a DSC (Shimadzu DSC-60 thermal analyzer, Japan). The instrument was calibrated using indium as standard. Samples (5 mg) were heated in sealed aluminum pans under nitrogen using the following program: hold for 10 min at 40°C and heat from 40.0 to 250.0°C at a scanning rate of 10°C/min. Then the samples were subjected to DSC studies. Samples were sealed in 40- μ L aluminum pans. An identical empty pan was used as a reference. The samples were scanned at 10°C/min with a 50 mL/min nitrogen purge.

RESULTS AND DISCUSSION

Phase solubility studies

The phase solubility profiles of fenofibrate-HP β CD are presented in Figure 1. This plot showed that aqueous solubility of the drug increases linearly as a function of HP β CD. The phase solubility profile of fenofibrate with HP β CD can be classified as A_L-type. The linear host-guest correlation coefficient $r=0.9969$ ($r^2=0.994$) with a slope (m) of 0.004 suggested the formation

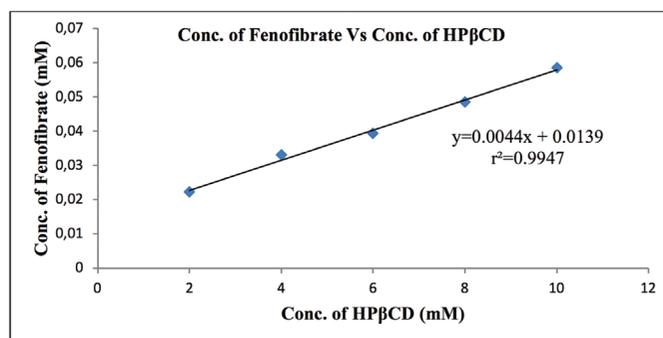


Figure 1. Phase solubility diagram of the fenofibrate-HP β CD system in water

HP β CD: Hydroxy propyl β -cyclodextrin

of a 1:1 complex with respect to HPβCD concentrations. The apparent stability constants, $K_{1:1}$, obtained from the slope of the linear phase solubility diagram was 630.0006 M^{-1} for HPβCD [Eq. (1)]. The $K_{1:1}$ value suggested that fenofibrate formed more stable complex with HPβCD.

An indication of the process of transfer of fenofibrate from pure water to the aqueous solution of HPβCD may be obtained from the values of the Gibbs free energy change (Table 1). The values of Gibbs free energy associated with the aqueous solubility of fenofibrate in the presence of HPβCD (were all negative for HPβCD at various concentrations, indicating the spontaneous nature of the drug solubilization. The values decreased with increasing HPβCD concentration, demonstrating that solubilization was more favorable as concentration of HPβCD increased.

Table 1. Effect of HPβCD concentration and Gibbs free energy on solubility of fenofibrate

Sr. no.	Concentration of HPβCD (mM)	Concentration of fenofibrate (mM)	(ΔGtr) (J/Mol)
1	0	0.007012	0
2	2	0.022256	-684.006
3	4	0.033079	-918.699
4	6	0.039483	-1023.508
5	8	0.048561	-1146.070
6	10	0.058632	-1257.683

HPβCD: Hydroxy propyl β-cyclodextrin

Dissolution studies

The results of the dissolution studies for individual samples (fenofibrate alone, PMs, and complexes) over 2 h are shown in Figure 2. Onset of dissolution of pure fenofibrate is very slow, with about 13.29% of drug being dissolved in 120 min. Complexes of fenofibrate with HPβCD had considerably enhanced dissolution rates as compared to pure drug fenofibrate and PMs.

Percentage dissolution efficiencies (%DE) values were computed for comparative analysis of all the formulations. The %DE values in the initial time period of the dissolution study, i.e.,

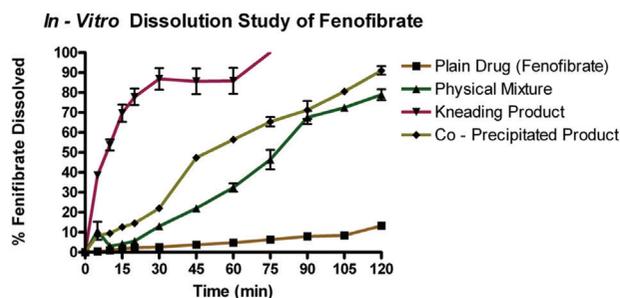


Figure 2. *In vitro* dissolution study of fenofibrate-HPβCD complexes

HPβCD: Hydroxy propyl β-cyclodextrin

%DE_{10min}, provide comparative information for very fast releasing formulations, whereas those for %DE_{60min} provide relative information about both fast and slow releasing formulations. The values of %DE_{60min} for the pure drug increased to 32.45% in PMs and up to 87.39% in kneaded product and 56.46% in coprecipitated products. The change in DE_{60min} of the drug in its PMs and complexes is statistically significant ($p < 0.05$).

The results of % dissolution and dissolution efficiency study indicate an improvement in the dissolution rate of fenofibrate in cyclodextrin complexes by both techniques. The improvement in dissolution rate is possibly caused by several factors:

- the strong hydrophilic character of HPβCD, which improves the water penetration and wettability of the hydrophobic fenofibrate,
- the optimal dispersion of fenofibrate to HPβCD,
- the absence of crystals corresponds to lower energy required for dissolution, and
- the intermolecular hydrogen bonds and the molecular dispersion of fenofibrate on HPβCD lead to partial miscibility, improving the hydrophilic characteristics of the drug substance via interactions with βCD the improvement of dissolution rate of fenofibrate in the physical mixture is due to increased wettability of the drug powder.²⁰

Kneading showed better dissolution than coprecipitation. This could be attributed to the improved wetting provided by cyclodextrins in kneading than in coprecipitation, as earlier reported by Mukne for triamterene²¹ and Deshmukh for ziprasidone.²² Thus it can be concluded that kneading is better for complexation than coprecipitation.

FTIR spectroscopy

The FTIR spectra of the systems of fenofibrate-HPβCD and those of pure components are shown in Figure 3. When the systems are compared, it can be observed that the ester group stretching band at 1727.91 cm^{-1} broadens and shifts towards higher wavenumbers, indicating change in the intermolecular H-bonds of the drug upon complexation. Similar modifications

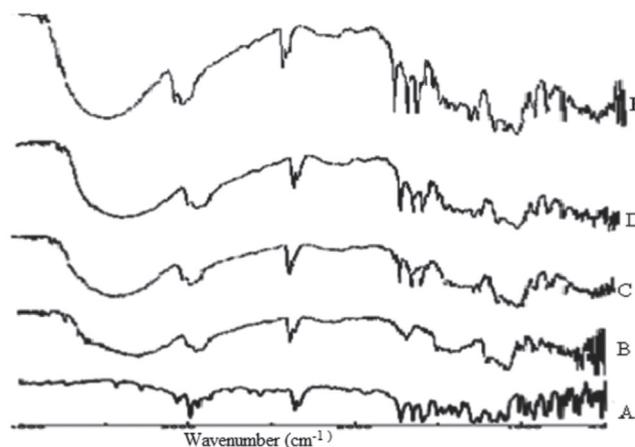


Figure 3. FTIR spectrograms of a) pure drug fenofibrate, b) HPβCD, c) physical mixture, d) kneading product, e) coprecipitated product

FTIR: Fourier transform infrared, HPβCD: Hydroxy propyl β-cyclodextrin

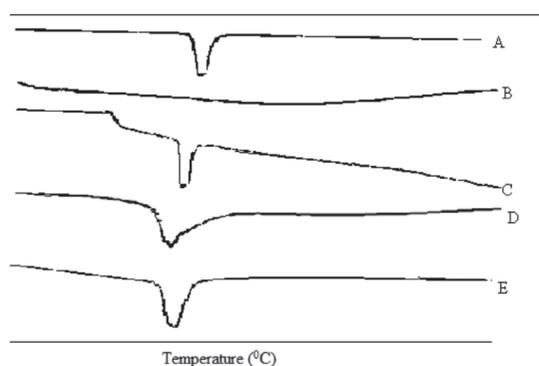


Figure 4. DSC curves of a) fenofibrate, b) HP β CD, c) physical mixture, d) kneading product, e) coprecipitation product

DSC: Differential scanning calorimetry, HP β CD: Hydroxy propyl β -cyclodextrin

were seen in the combination signal of the ester group, which indicates change in the interaction of this group when the complex is formed. In addition, the bands at 1050–1340 cm^{-1} corresponding to antisymmetric vibrations of the aryl ether group and C–O stretching of esters broaden in some cases and in others peaks vanish upon complexation. The decreased intensity and vanishing of the band are associated with the out-of-plane bending of the aromatic C–H bonds at 824–844 cm^{-1} , evidence of the inclusion of the benzene ring.²³

Finally, the C–H stretching seen at 3032–3052 cm^{-1} vanishes in the complexes, indicating that complexation has occurred.

DSC studies

The DSC thermogram of HP β CD showed a straight line. The DSC curve of fenofibrate showed a broad endothermic peak in the range of 80–90°C owing to the melting point of the drug. The peak of fenofibrate showed changes in terms of peak area and ΔH (heat of fusion) value (Table 2) in the case of the complexes as compared to the physical mixture comprising drug:HP β CD in the same ratio. This suggested that the presence of HP β CD resulted in complexation of fenofibrate. The change in peak height and broadening of peaks may be attributed to loss of crystallinity.²⁴

Table 2. Peak area and heat of fusion (ΔH) values obtained from DSC curves

Sample	Height mW	ΔH (J/gm)
Fenofibrate	-8.82	93.83
Physical mixture (P1)	-5.35	20.21
Kneading product (B1)	-2.44	12.03
Coprecipitation product (C1)	-3.41	12.7

DSC: Differential scanning calorimetry

CONCLUSIONS

The solubility and dissolution rate of fenofibrate can be enhanced by the use of complexes of fenofibrate with HP β CD. The solubilization effects of HP β CD, reduction of particle

aggregation of the drug, loss in crystallinity, increased wettability and dispersibility, and alteration in the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of fenofibrate from its complexes and physical mixtures.

Kneading showed better dissolution than coprecipitation. This could be attributed to the improved wetting provided by cyclodextrins in kneading than in coprecipitation.

It is concluded that fenofibrate–HP β CD complexation results in an increase in the solubility and dissolution rate of the drug, suggesting a possible enhancement of its oral bioavailability.

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Conflict of Interest: No conflict of interest was declared by the authors.

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