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Effect of Hydrophilic Polymer on Solubilization of Fenofibrate by Cyclodextrin Complexation

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Abstract

The present work investigates the possibility of improvement of the complexation efficiency of cyclodextrin towards a drug by adding a third auxiliary component (hydrophilic polymer). Phase solubility Analysis at 25 °C was used to investigate the interaction of the drug in both the binary systems (viz. Drug-Cyclodextrin and Drug-Polymer) and the ternary system (Drug-Cyclodextrin-Polymer). The combined use of polymer and cyclodextrin was clearly more effective in enhancing the aqueous solubility of the fenofibrate in comparison with the corresponding drug-cyclodextrin or drug-polymer binary systems. Hydrophilic polymers increased the complexation efficacy of cyclodextrin towards fenofibrate (as shown by the increased stability constants of the complexes). Polyvinyl Pyrollidone (PVP) was found to be most effective in enhancing the solubilization of fenofibrate by β-Cyclodextrin, the best results were obtained in ternary system with β-Cyclodextrin in presence of 1%w/v (PVP). Formulated ternary system with optimized drug:cyclodextrin:polymer ratio of 1:3.5:1 w/w resulted in a significant improvement in the dissolution rate of fenofibrate and showed 90% dissolution efficiency (D.E) as compared to around 15% and 83% of the plain drug and binary system respectively. DSC studies was carried out to characterize the ternary complex.

Introduction

When a cyclodextrin forms a complex with a drug, the complexation efficiency can be considered equal to the product of the intrinsic solubility of the drug (So) and the stability constant of the complex (Ks) [1]. Thus, increased complexation efficiency can be obtained by increasing So, Ks, or both simultaneously.

Recent works have shown that the presence of various auxillary substances mainly hydrophilic polymers can significantly affect cyclodextrin complexation [2]. Hydrophilic polymers used in combination with cyclodextrin tend to increase the complexation efficiency by increasing both the intrinsic solubility of the drug as well as the stability constant of the complex.

The present work investigates the effect of hydrophilic polymers on complexation efficiency of cyclodextrin towards fenofibrate. Combined effect of various hydrophilic polymers (Polyvinyl pyrollidone [PVP], Hydroxy propyl methyl cellulose[HPMC], Polyethylene glycol 4000 and 6000 [PEG 4000 & PEG 6000]) and β-cyclodextrin on solubilzation of fenofibrate was studied. Fenofibrate, an anti hyperlipidemic agent, was selected as the model drug as it has extremely poor water solubility (< 0.1 μg/ml) [3–5].

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The present work throws light on solubility enhancement of fenofibrate by β-cyclodextrin in presence of hydrophilic polymers and formulation of a ternary system of fenofibrate with β-cyclodextrin and hydrophilic polymer.

Experimental

Materials

Fenofibrate (FEN) was supplied by Cipla Ltd. Mumbai, India. β-Cyclodextrin was generously donated by Cerestar USA, Inc., IN. All the reagents and solvent used were of analytical grade.

Methods

Phase solubility studies

Phase solubility equilibrium diagrams (in water at 25 °C) were obtained for both binary and ternary systems according to Higuchi and Connors [6]. Studies for binary systems were carried out by adding an excess amount of the drug to 25 ml aqueous solutions containing increasing concentrations of β-cyclodextrin (from 0% to 1.85% w/v, i.e., to its saturation solubility at 25 °C) or polymers (from 0% to 1.5% w/v). Experiments for ternary systems

were performed analogously to those for the binary systems, but in presence of a fixed amount of the third component (i.e. 1% w/v polymer). This series of suspensions were equilibriated for 48 h on a mechanical shaker. All the suspensions were then filtered and assayed for drug concentration.

Preparation of ternary complex

Ternary complex comprising of Drug:β-Cyclodextrin: Polymer in the ratios 1:3.5:0.5, 1:3.5:1 and 1:3.5:1.5 w/w were prepared using kneading method. Physical Mixture (PM) of Drug:β-Cyclodextrin:Polymer in the ratio 1:3.5:1 was prepared by mixing in geometric proportion followed by passing through No. 80 sieve with minimum abrasion. The ternary systems were prepared by first dissolving the drug and the polymer in organic solvent followed by kneading with β-Cyclodextrin to get a pasty consistency. The mass was then dried overnight at 40 °C. The dried powder was passed through No. 80 sieve and stored in a vacuum dessicator until further use.

In-vitro *dissolution studies*

Dissolution studies of samples were performed in 900 ml of 20 mM SLS at 37 ± 0.5 °C using USP XXIII type II apparatus. The samples were withdrawn at predetermined intervals and analyzed spectropotometrically (Jasco model 530 S) at 289 nm.

Differential Scanning Calorimetry (DSC) studies

The samples were subjected to DSC studies using (Perkin Elmer pyris 4 series). Samples were sealed in 40 μl aluminium pans. An identical empty pan was used as a reference. The samples were scanned at 5 °C/min with a 20 ml/min nitrogen purge.

Results and discussion

Influence of polymers on the solubility of the drug

Literature survey reveals the solubilizing effect of hydrophilic polymers toward a number of drugs through the formation of water-soluble complexes [7–8]. Therefore, equilibrium solubility studies were performed in aqueous solutions to determine the solubilizing effect of different polymers on FEN. All the examined polymers showed a solubilizing effect towards FEN, which could be attributed to weak polymer drug interactions. In all cases, the optimal polymer concentration was found to be 1% w/v since further addition of polymer led to no further increase in drug solubility (Figure 1). PVP K-30 showed the maximum increase in the solubility as compared to other polymers.

Effect of polymers on the stability constants of complexes

The phase solubility diagrams of FEN in aqueous solutions at 25 °C of β-Cyclodextrin, with or without 1% w/v of polymers, were all of Higuchi's A_L type: that

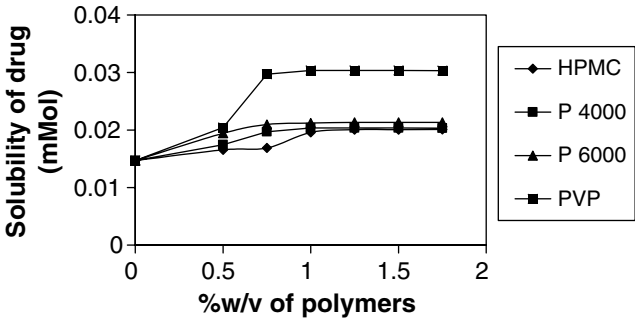

Figure 1. Phase solubility curves of various drugs: polymer binary systems. Where, HPMC = Hydroxy propyl methylcellulose. P 4000 = Polyethylene Glycol 4000. P 6000 = Polyethylene Glycol 6000. PVP = Poly vinyl Pyrollidone.

is a linear increase of drug concentration was observed as a function of cyclodextrin concentration, independent of the presence of polymer. The slopes in all cases were less than unity, thus confirming the formation of 1:1 complexes (6). The values of stability constants of FEN-CD complexes, both when no polymer was present or in the presence of 1% w/v polymer are shown in Table 1. Addition of the polymer always resulted in an increase in the stability constant, which could be attributed to the increase of the cyclodextrin complexing power towards FEN. Addition of polymers could contribute to improvement of the complexation ability of cyclodextrins by establishing interactions such as hydrophobic bonds, vander Waals dispersion forces, or hydrogen bonds and/or promoting the release of high-energy water molecules present in their cavity [9]. PVP K-30, which exhibited the highest solubilizing effect in binary systems, likewise showed the largest enhancing effect on cyclodextrin FEN solubilization as compared to other tested polymers as evident by a large increase in stability constant.

Effect of Polymer-Cyclodextrin combination on drug solubility

The effect of different polymer-cyclodextrin combinations on the aqueous solubility of FEN is presented in Table 2. Solubility of FEN in aqueous solutions at 1.85% w/v β-CD was about 10 times higher than in water. The addition of 1% w/v of water-soluble polymers to the solution medium improved the drug

Table 1. Effect of various polymers on stability constant of complex

Polymer	Ks (M^{-1})	Kst/Ksb
No Polymer	106.806	–
HPMC	121.236	1.135
PEG 4000	157.931	1.4786
PEG 6000	194.017	1.816
PVP	220	2.059

where, Ks = Stability constant; Ksb = Stability constant of drug/cyclodextrin binary system; Kst = Stability constant of drug/cyclodextrin/polymer ternary system.

Table 2. Effect of polymers on solubilization of Fenofibrate (FEN) in aqueous B-CD solutions (16.29 mM solution) at 25 °C

Polymer	S_1 (μg/ml)	S_2 (μg/ml)	S_2/S_0
HPMC	4.14	51.04	1.39
PEG 4000	5.25	59.81	1.53
PEG 6000	5.74	61.23	1.57
PVP	10.04	92.548	2.37

HPMC, hydroxy propyl methylcellulose; PEG 4000, polyethylene glycol 4000; PEG 6000 = polyethylene glycol 6000; PVP, poly vinyl Pyrollidone. S_1 = Solubility of FEN in aqueous solution containing 1% w/v polymer. S_2 = Solubility of FEN in aqueous solution containing 1% w/v polymer and 1.85%w/v B-CD. S_0 = Solubility of FEN in aqueous solution containing 1.85%w/v B-CD (36.74 μg/ml). S_2/S_0 = Solubility ratio.

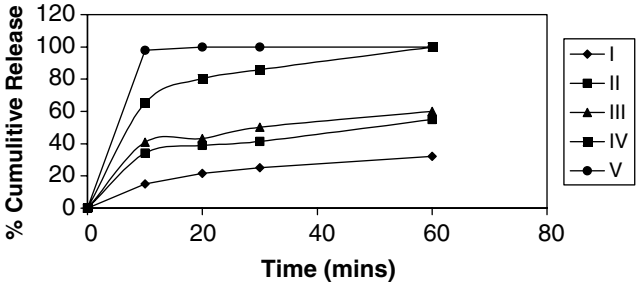

Figure 2. Dissolution profiles of fenofibrate from various systems. I = Plain Drug. II = Drug-BCD (1:3.5 w/w) Physical Mixture. III = Drug-BCD-PVP (1:3.5:1 w/w) Physical Mixture. IV = Drug-BCD (1:3.5 w/w) complex. V = Drug-BCD-PVP (1:3.5:1 w/w) Ternary Complex.

solubility even further. As previously seen, polymers themselves showed a solubilizing effect on FEN. However, when polymer and cyclodextrin are present together in the solution, one achieves an extent of drug solubilization greater than when they are used separately. The highest enhancements were obtained for ternary systems with β-CD in presence of 1% w/w PVP K-30 and thus, the ternary complex was formulated using PVP K-30 as the third component.

Evaluation of formulated ternary complex

Dissolution studies were performed in dilute surfactant solutions so that the sink conditions were maintained. The results obtained are presented in Table 3. The ratio of polymer (PVP K-30) in the ternary complex was optimized based on the results from dissolution studies. A ratio of 1:3.5:1 w/w (drug: β-CD: PVP) was found to be the best combination as evident from the drug release studies (Figure 2). Ternary complex also showed a D.E. of 90% as compared to around 15% and 83% in case of plain drug and FEN-BCD complex respectively.

The DSC thermograms of Fenofibrate, β-Cyclodextrin, Polyvinyl Pyrollidone, physical mixture and the ternary complex are illustrated in Figure 3. The DSC thermogram of fenofibrate showed a sharp endothermic peak at 82 °C, which represents its melting point. The DSC thermogram of β-Cyclodextrin showed a broad endotherm in the range of 100–120 °C, which can be attributed to the release of water molecule from the cavity (desolvation). The DSC curve of PVP showed a broad endothermic peak in the range of 50–60 °C owing to the softening of the polymer. The peak of fenofibrate showed changes in terms of peak area and ΔH (heat flow) value (Table 4) in case of the ternary complex as compared to the physical mixture comprising of drug: β-CD:PVP in the same ratio as that of ternary complex (i.e 1:3.5:1 w/w). This suggested that the presence of polymer resulted in higher complexation of fenofibrate by cyclodextrin in the ternary complex thus resulting in higher dissolution rate of fenofibrate and an increased dissolution efficiency of the system.

Conclusion

Our study confirmed that the addition of small amounts of hydrophilic polymers improves the solubilizing and complexing ability of cyclodextrin. All the examined polymers (PVPK30, HPMC, PEG 4000 and PEG 6000) showed an evident improvement effect on FEN cyclodextrin solubilization by increasing complexation efficacy. The highest solubility improvement was obtained for ternary system of FEN-β-CD in presence

Table 3. Results from the *In-vitro* dissolution studies of various systems

Ternary System (Drug:Cyclodextrin: Polymer)	Dissolution Percentage D.P 15 min (%)	Dissolution Efficiency D.E 30 min (%)
Optimization of ratio of polymer in ternary complex		
1:3.5:0.0 w/w	77.46	82.95
1:3.5:0.5 w/w	84.09	84.46
1:3.5:1.0 w/w	100.00	90.00
1:3.5:1.5 w/w	100.00	90.52
Systems	Dissolution Percentage D.P 15 min (%)	Dissolution Efficiency (D.E.) 30 min (%)
Evaluation of drug release in terms of D.E and D.P		
Plain Drug	20.12	14.35
Drug:BCD (1:3.5 w/w) P.M	39.27	26.58
Drug:BCD: PVP (1:3.5:1) P.M	42.12	35.09
Drug:BCD (1:3.5 w/w) complex	77.46	82.95
Drug:BCD: PVP (1:3.5:1) complex	100.00	90.00

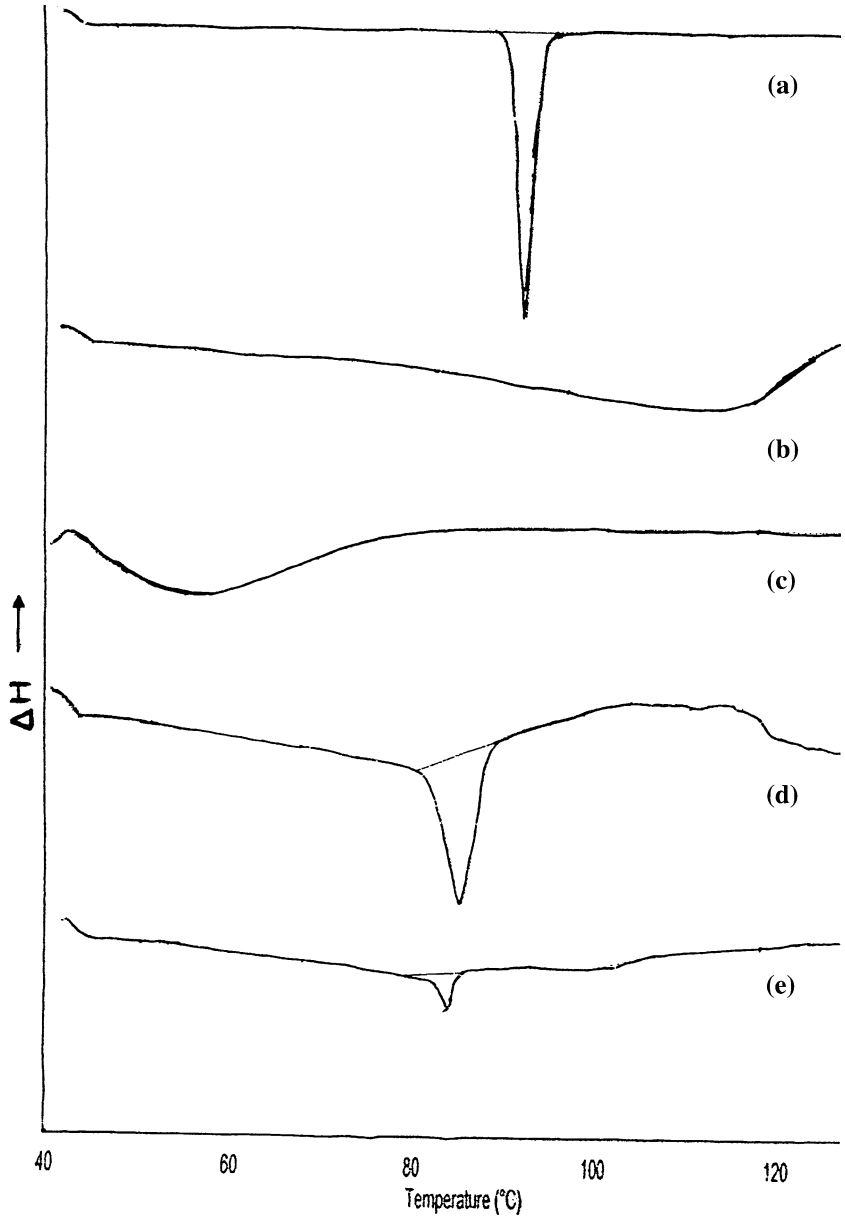

Figure 3. DSC curves of (a) Fenofibrate (b) β-Cyclodextrin (c) Polyvinyl Pyrollidone (PVP) (d) Physical Mixture (PM) {Drug:β-CD:PVP (1:3.5:1 wt/wt)} (e) Ternary complex [Drug:β-CD: PVP (1:3.5:1 wt/wt)].

of 1% w/w PVP K-30. Such a result can probably be attributed to the contemporaneous favorable effect of the polymers on the aqueous solubility of β-CD.

Table 4. Peak area and delta H values obtained from DSC curves

	Peak Area (mJ)	Delta H (J/g)
Fenofibrate	565.779	113.155
Physical mixture	519.663	51.966
Binary complex	154.764	15.234
Ternary complex	66.371	6.637

Physical Mixture = FEN: B-CD: PVP (1:3.5:1 w/w). Binary Complex = FEN: B-CD (1:3.5 w/w). Ternary Complex = FEN: B-CD: PVP (1:3.5:1 w/w).

Formulated ternary system with optimized drug:cyclodextrin:polymer ratio of 1:3.5:1 w/w resulted in a significant improvement in the dissolution rate of fenofibrate. Ternary System also showed 90% D.E. as compared to around 15% and 83% of the plain drug and binary system respectively. Characterization studies suggested the formation of ternary system.

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