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Original Article

The Effect of Water Soluble Polymers on Felodipine Aqueous Solubility and Complexing Abilities with Natural and Modified β-Cyclodextrin

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Abstract

Purpose of this study was to investigate the effect of the presence of the water soluble polymers viz HPMC, PVP and PEG 6000 on aqueous solubility and complexation abilities of felodipine with or without presence of β-cyclodextrin (βCD) and HPβCD by phase solubility studies. The data revealed the initial increase in drug solubility followed by plateau in the presence of relatively low polymer concentration i.e. 0.25-0.5 %w/v. Phase solubility diagrams of felodipine in ternary system showed similar behaviour to binary system without βCD. Addition of water soluble polymer to βCD solution improved βCD solubilizing efficiency due to increase in βCD complexing power toward felodipine. In binary system solubility was found 2.5 to about 10 times higher than in water which was further improved in the presence of 0.25% w/v water soluble polymer. Ternary systems with βCD showed highest increments in solubility towards felodipine, with 78.8%, 81.8% and 74% improvement after the addition of 0.25% w/v HPMC, PVP and PEG6000, respectively. Our study confirmed that addition of small amounts of hydrophilic polymer is useful strategy for improving the solublization and complexing abilities of cyclodextrins thus allowing less cyclodextrin to be needed to solubilize given amount of drug. This offers economic advantage. All the polymers under study showed synergistic effect on felodipine cyclodextrin solublization by increasing complexation efficiency.The highest solubility improvement up to 81.8% was obtained for βCD ternary system when 0.25% w/v of PVP was used.

Keywords: Complexation; Cyclodextrin; Felodipine; Water soluble polymers.
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1. Introduction

Cyclodextrins (CDs) are cyclic molecules consisting of six (αCD), seven (βCD) or eight (γCD) glucose units linked through α-1, 4 linkages. These ring shaped molecules enclose cavities of approximately 5-8 A° in diameter [1]. These are torus shaped molecules with hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As the consequences of

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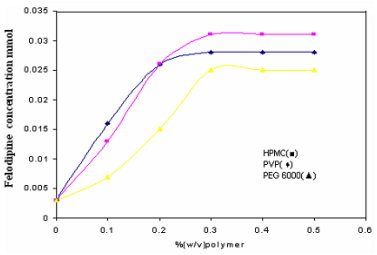

Figure1. Effect of increasing concentration of HPMC (■), PVP (♦), PEG 6000(▲) on aqueous solubility of felodipine at 25 °C.

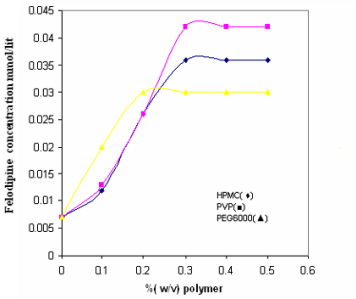

Figure2. Effect of increasing concentration of HPMC (♦), PVP (■) and PEG 6000(▲) on aqueous solubility of felodipine in presence of 1.6%w/v βCD (saturation solubility).

inclusion phenomenon many physicochemical properties such as solubility, dissolution rate, stability and bioavailability can be favorably modulated [2-4]. However, various reasons such as their high molecular weight, relatively low water solubility and toxicity of the parent CDs limit their further application in pharmaceutical formulation [5]. Therefore, in cases where the low complexation efficiency would require a large amount of cyclodextrin (CD) than the acceptable amount for solid or liquid dosage forms, the enhancement of complexation capacity of chosen CD is of practical importance [6]. When CD forms a complex with drug, the complexation efficiency can be determined by either the slope of phase solubility profile or complex to free cyclodextrin concentration ratio [7].

Typical pharmaceutical preparations are complex mixtures of drugs and excipients, which can include vehicle additive, osmolality modifiers, pH modifiers, surfactants, preservatives, organic solvents, and very often reducers of the complexation efficiency [1]. In contrast, significant increase in apparent stability constant of drug-CD complex has been obtained through formation of drug-hydroxy acid CD ternary complexes or salts with basic drugs. Similarly, enhanced complexation is obtained by the addition of small amounts of various water soluble polymers to form ternary complexes between drug, CD and third component [1].

Felodipine is a dihydropyridine calcium antagonist widely used as a potent antihypertensive drug. However, the oral bioavaibility of felodipine is very low because of the first pass effect [8]. Felodipine is poorly water soluble and dissolution could be a rate limiting process for absorption of drug. Many technological methods regarding enhancement of dissolution characteristics of drugs with low water solubility has been reported such as micronization, formation of solvates, complexes, microspheres and solid dispersions [9].

The aim of our investigation was to study combined effect of various hydrophilic polymers (HPMC, PVP, and PEG 6000) and

Table1. Effect of polymers (0.25% w/v) on the stability constant (Ks) of felodipine complexes with different cyclodextrin in aqueous solutions at 25 °C.

Polymer	βCD			HPβCD		
	Ks (M^{-1})	K_{st}/K_{sb} [a]	CE	Ks (M^{-1})	Kst/K_{sb} [a]	CE
No polymer	156.74		0.0004	690.00		0.0020
HPMC	668.00	4.26	0.0020	768.45	1.11	0.0022
PVP	668.00	4.26	0.0024	1003.00	1.45	0.0029
PEG6000	634.60	4.04	0.0012	710.00	1.03	0.0021

[a] Ratio between stability constants of ternary (Kst) and binary (Ksbs) systems.

cyclodextrins (βCD, HPβCD) on complexation efficiency and aqueous solubility enhancement of felodipine.

2. Materials and methods

Felodipine was obtained as gift sample from Cipla Pvt Ltd, Mumbai, βCD was obtained from Roquette Services Techniques ET Laboratories France, HPβCD was obtained from SA Chemicals Mumbai. HPMC E5, PVP, and PEG 6000 were obtained from Loba Chemie, India. All other chemicals used were of pharmaceutical or special analytical grade.

2.1. 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 [10]. Studies for binary systems were carried out by adding excess amount of drug to 10 ml aqueous solution containing increasing concentration of cyclodextrin from 0 to 7.5%w/v for HPβCD or from 0 to 1.6 %w/v for βCD or polymer from 0 to 0.5 %w/v. Experiments for ternary systems were performed similarly to those for binary systems but in presence of fixed amount of one component, that is polymer (0.25% w/v) and cyclodextrin (7.5 % w/v for HPβCD and 1.6 % w/v for βCD) respectively. The glass containers were sealed and electromagnetically stirred at constant temperature until equilibrium was reached (48 h). An additional series of suspension containing excess amount of drug in presence of 0.25% w/v polymer and 7.5%w/v HPβCD or 1.6% w/v of βCD was sonicated for 1hr in ultrasonic bath and heated for 2h in oven at 90°C and then equilibrated under electromagnetic stirring at 25 °C for 48h. All suspensions were then filtered through 0.45 μm membrane filter and assayed for drug content by UV visible spectrophotometer at 364 nm.

The apparent stability constant of felodipine - CD complexes were determined from slope of phase solubility diagrams.

2.2. Complexation efficiency or solublizing efficiencies

It is determined by either the slope of phase solubility profile or complex to free cyclodextrins concentration ratio [7].

$$CE = [D/CD] / [CD] = S_\circ * K (1:1) = Slope / 1\text{-}Slope \quad \text{(Equation 1)}$$

Where CE, complexation efficiency; $S_\circ$, intrinsic solubility; K, stability constant; [D/CD], concentration of dissolved complex; [CD], concentration of dissolved free βCD.

3. Results

3.1 Influence of polymers

Several papers have been reported the solublizing effect of hydrophilic polymers towards a number of drugs through formation of water soluble complexes [6, 8, 11-15]. Therefore equilibrium solubility studies were

Table2. Effect of polymers on solublization of felodipine in aqueous cyclodextrin solution at 25 °C

	Polymer	S_{cd}(mg/l)[a]	S_{pol}(mg/l)[b]	S_{cd+poi} (mg/l)[c]	S_{cd+pol}/S_{cd}[d]
βCD	HPMC	3	12.0	14.20	4.70
	PVP		11.0	16.50	5.50
	PEG6000		9.6	11.90	3.96
HPβCD	HPMC	12	12.0	13.80	1.57
	PVP		11.0	18.00	2.00
	PEG6000		9.6	13.00	1.40

HPMC: hydroxy propyl methyl cellulose, PVP: poly vinyl pyrrolidone, PEG: poly ethylene glycols.
[a]Solubility in aqueous solution containing 1.6% w/v βCD or 7.5% w/v βCD derivatives.
[b]Solubility in aqueous solution containing 0.25% w/v polymer.
[c]Solubility in aqueous solution containing both polymer and cyclodextrin.
[d]Solubility ratio.

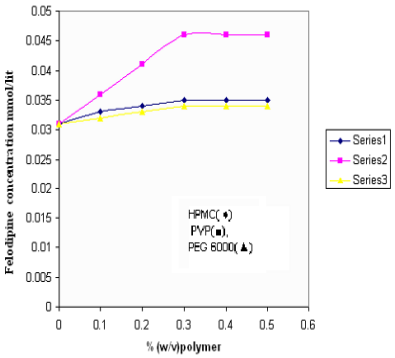

Figure3. Effect of increasing concentration of HPMC (♦), PVP (■), PEG 6000(▲) on aqueous solubility of felodipine in presence of 7.5% w/v βCD derivative.

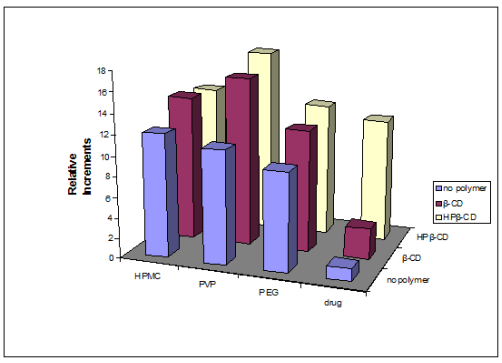

Figure 4. Relative solubility increase of felodipine in aqueous solution at 25 °C containing 7.5%w/v HPβCD or 1.6%w/v βCD alone or in presence of 0.25% w/v of different polymer.

performed in aqueous solutions to determine solublizing effect of different polymer on felodipine. In all cases an initial increase in drug solubility was observed but it was rapidly followed by plateau that was achieved in presence of relatively low polymer concentration (0.25-0.5% w/v). It is showed in Figure1.

3.2. Influence of association - polymer and cyclodextrin

Phase solubility diagrams of felodipine in ternary systems obtained by adding an excess of drug to aqueous solution containing increasing amounts of polymer and a constant amount of cyclodextrin (Figures 2 and 3) showed behaviour similar to that of corresponding binary systems without cyclodextrin. In fact, in most cases, a plateau was rapidly established, even though it was at higher felodipine concentration level owing to the presence of cyclodextrin. All the polymers showed a different solublizing effect depending on type of cyclodextrin present in aqueous solution.

3.3. Effect of polymer on stability constant of complexes

The phase solubility diagrams of felodipine in aqueous solution at 25 °C of two different cyclodextrins, with or without 0.25% w/v of polymer, were all of Higuchis A_L type *i.e.* a linear increase of drug concentration was observed as function of cyclodextrin. The slope in all cases was less than unity thus confirming the formation of 1:1 complex.

The values of apparent stability constants of felodipine CD complexes, both in presence or absence of 0.25% w/v polymer are shown in Table 1. Addition of polymer to the cyclodextrin solution always resulted in increased stability constant. Therefore the improved cyclodextrin solublizing efficiencies can be attributed to the increased cyclodextrin complexing power toward felodipine.

3.4. Effect of polymer, cyclodextrin and their combination on drug solubility

The effect of different polymers, cyclodextrins and their combinations on aqueous solubility of felodipine is presented in Table 2. Solubility of felodipine in aqueous solution at 7.5% w/v βCD derivative or 1.6% w/v native βCD was found to be 2.5 times to about 10 times (for HPβCD)higher. The addition of 0.25% w/v of water soluble polymer to the solution medium improved the drug solubility even further.

The highest increments were obtained for ternary systems with βCD, with solublizing effect towards felodipine that improved 78.8%, 81%, 74% when 0.25% w/v of HPMC, PVP, PEG 6000 respectively was present. On the contrary lower increment

ranging from 13%, 33.33%, and 7.6% for HPMC, PVP, and PEG6000 polymers respectively were obtained with βCD derivatives. Relative increments in solubility of felodipine with respect to CDs and water soluble polymers showed in Figure 4.

4. Discussion

Water soluble polymers influenced increase in felodipine solubility. It is evident that, as consequences of drug carrier interactions all examined polymer showed an increased solublizing effect toward felodipine. As early discussed in literature hydrophilic polymers mainly interact with drug molecules by electrostatic bonds *i.e.* ion to ion, ion to dipole and dipole-dipole bonds and even through other types of forces such as Vander walls forces and hydrogen bridges to form complexes. Differences in conformational structure, degree of polymerization, charge density, accessibility and type of functional groups on polymer chain could account for different solublizing power toward felodipine as presented by considered polymer.

As an influence of association *i.e.* polymer and cyclodextrin results showed further increase in solubility of felodipine. This indicated that more or less intense interactions between the polar groups of each polymer, felodipine and CD molecules. Felodipine CD molecules are responsible for the different pattern of solubility's shown by polymer in combination with various cyclodextrins.

Stability constants of felodipine-CD complexes in presence of water soluble polymers were found to be increased which indicated that addition of polymer contribute to favoring complexation ability of cyclodextrins by establishing interactions such as hydrophobic bonds, van der Walls dispersion forces, hydrogen bonds and/or by promoting the release of high energy water molecule present in their cavities [13].

Solubility studies on binary systems *i.e.* felodipine-CD, Felodipine-polymer showed improved drug solubility. These results reveled that solubility studies on binary system showed definite interaction between felodipine and each CD and between felodipine and each examined polymer, suggesting that formation of polymer-felodipine soluble complexes in solution. Thus possible interaction in ternary systems, in addition to those already present in binary system are in regard to felodipine-CD-polymer, polymer-felodipine-CD systems and possible inter polymer complexation between polymer and CD.

Nowadays, cyclodextrins are widely accepted as formulator's option in drug development due to its extreme usefulness as excipients, availability in pure form, reasonably cost and acceptance by various regulatory.

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