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# EFFECT OF PVA ON HP –β- CD INCLUSION COMPLEXES OF DICLOFENAC FOR ENHANCING ITS DISSOLUTION RATE

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## ABSTRACT

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. Among the various techniques, cyclodextrin complexation is an efficient approach for enhancing the dissolution rate and bioavailability of BCS – Class II Drugs. Diclofenac, a widely prescribed NSAID is poorly soluble in aqueous fluids and exhibits low and variable oral bioavailability. Solid inclusion complexes of diclofenac - HPβCD in 1:1 and 1:2 ratios were prepared with and without PVA by three methods namely - physical mixing, kneading and solvent evaporation. All the complexes prepared were found to be fine and free flowing powders. The dissolution of diclofenac was rapid and higher from all the cyclodextrin inclusion complexes prepared when compared to diclofenac pure drug. The dissolution data obeyed first order kinetic model as well as Hixson-Crowell's cube root model in all the cases. All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than diclofenac indicating rapid and higher dissolution of diclofenac from its CD complexes. The $K_1$ and $DE_{20}$ values were increased as the proportion of CD in the complex systems was increased in each case. Complexes prepared by kneading method gave higher dissolution rate and $DE_{20}$ values than those prepared by co-precipitation and physical mixing methods. Diclofenac–HPβCD (1:4) kneaded complex gave a 24.13 fold increase in the dissolution rate of diclofenac, whereas in the presence of PVA, diclofenac – HPβCD - PVA (1:1:0.25), gave a 42.6 fold increase in the dissolution rate of diclofenac. As the concentration of the hydrophilic carrier in the inclusion complex increased, the dissolution rate of the drug also increased. Because of the enhancement in cyclodextrin complexation and dissolution rate by the presence of PVA, a low amount of CD can be used to get the desired dissolution rate and efficiency.

**Keywords:** Diclofenac, Cyclodextrin complexation, PVA, Dissolution rate.

## INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters and pose challenging problems in their pharmaceutical product development process. Efavirenz belongs to Class II under BCS and exhibit low and variable bioavailability due to its poor aqueous solubility. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy.

Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles and nanosuspensions, micro emulsion and self-emulsifying systems are available[1] to enhance the bioavailability of BCS Class II drugs. Among the various techniques, cyclodextrin complexation is an efficient approach for enhancing the dissolution rate and bioavailability of BCS – Class II Drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability, palatability and bioavailability can be favorably affected[2,3] without affecting their physio-chemical properties. Cyclodextrins have been receiving increasing application in pharmaceutical products in recent years due to their approval by various regulatory agencies.[4,5] It is reported in a few studies [6,7] that addition of small amounts of water soluble polymers such as PVP, HPMC, PEG to cyclodextrin systems has improved both the complexing and solubilizing efficiencies of CDs. Diclofenac, a widely prescribed NSAID is poorly soluble in aqueous fluids and exhibits low and variable oral bioavailability because of its poor aqueous solubility. Hence the objective of the present study was aimed at enhancing the solubility and dissolution rate of diclofenac employing HP-βCD alone and with PVA.

## EXPERIMENTAL

**Materials and Methods:**

Diclofenac was a gift sample from M/s. Dr. Reddys Ltd., Hyderabad). Hydroxypropyl β- cyclodextrin was a gift sample from M/s Cerestar Inc., USA. Hydroxy Propyl Methyl Cellulose 6cps was a gift sample from Orchid Healthcare Pvt. Ltd., Chennai. Polyvinylalcohol (PVA, Sigma Chemical Co.), Methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

**Estimation of Diclofenac:**

An UV Spectrophotometric method based on the measurement of absorbance at 276 nm in phosphate buffer of pH 7.2 was used for the estimation of diclofenac. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative standard deviation was found to be less than 1.0%. No interference by the excipients used in the study was observed.

**Preparation of Solid Inclusion Complexes:**

In each case solid inclusion complexes of drug and cyclodextrins were prepared in 1:1, 1:2 and 1:4 ratio by three methods namely, kneading, solvent evaporation and physical mixing with and without the addition of PVA. In the series with PVA polymer, the polymer was added at a ratio of 0.25 and 0.5 by weight of the solid complex.

**Kneading Method:**

Drug (diclofenac), cyclodextrin and hydrophilic polymers were triturated in a mortar with a small volume of a solvent blend of water: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

**Solvent Evaporation Method:**

Drug (diclofenac) and carrier were dissolved in a common solvent (ethanol) and solvent was evaporated to form the solid mass. The contents were dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

**Physical Mixing:**

The physical mixtures of different ratios were prepared by mixing powders of drug (diclofenac), cyclodextrin and hydrophilic polymer in a dry mortar and the powder was sieved through mesh No. 120.

**Estimation of Drug Content of Solid Dispersions:**

From each batch four samples of solid dispersion equivalent to 20mg of the medicament were taken into 100 ml conical flasks and extracted with 3 x 10 ml quantities of methanol. The methanolic extracts were filtered and collected into 50 ml volumetric flasks. The volume of each solution was made up to 50 ml with methanol. The solutions were subsequently diluted with water and assayed for the drug content at 276 nm.

**Dissolution Rate Study:**

The dissolution rate of diclofenac as such and from CD complexes prepared was studied in 900 ml of phosphate buffer of pH 7.2 using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37±1$^{o}$C was maintained throughout the study. Drug or drug-CD complex equivalent to 25 mg of diclofenac was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45μ) at different intervals of time, suitably diluted and assayed at 276 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

## RESULTS AND DISCUSSION

Solid inclusion complexes of diclofenac - HPβCD in 1:1 and 1:2 ratios were prepared with and without PVA by three methods namely (i) physical mixing, (ii) kneading and (iii) solvent evaporation. All the complexes prepared were found to be fine and free flowing powders. There was no significant loss of drug during the preparation of solid inclusion complexes in all methods. Low R.S.D values (< 1.5%) in the percent drug content ensured uniformity of drug content in each batch.

The dissolution rate of diclofenac from CD complex systems prepared was studied in phosphate buffer of pH 7.2. The dissolution of diclofenac was rapid and higher from all the cyclodextrin inclusion complexes prepared when compared to diclofenac pure drug. The dissolution data were analyzed as per zero order, first order and Hixson-Crowell's cube root model to assess the kinetics and mechanism of dissolution. The dissolution data obeyed first order kinetic model as well as Hixson-

Crowell's cube root model in all the cases. The correlation coefficient (r) values were higher in the first order model than in zero order model indicating that the dissolution of diclofenac as such and from its CD complexes followed first order kinetics. The correlation coefficient (r) values of Hixson-Crowell's cube root model were found to > 0.8 indicating a change in surface area and diameter of the inclusion complexes. The dissolution data of all inclusion complexes prepared obeyed Hixson-Crowell's cube root model indicating that the dissolution of diclofenac has occurred from discretely suspended solid dispersions. This is because the Hixson-Crowell's cube root model is applicable to describe the dissolution of discrete particles of uniform size.

The first order dissolution rates ($K_1$) were calculated from the slopes of the corresponding linear plots. Dissolution efficiency ($DE_{30}$) values were calculated as per Khan[8]. $T_{50}$ (time taken for 50% dissolution) values were recorded from the dissolution profiles. Hixson-Crowell's rate constants were calculated from the slopes of the corresponding linear plots. The dissolution parameters and Hixson – Crowell's rate constants are summarized in Tables 1 and 2.

All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than diclofenac indicating rapid and higher dissolution of diclofenac from its CD complexes. The $K_1$ and $DE_{20}$ values were increased as the proportion of CD in the complex systems was increased in each case. The increase in $K_1$ (no. of folds) with various CD system is shown in Table 3. Complexes prepared by kneading method gave higher dissolution rate and $DE_{20}$ values than those prepared by co-precipitation and physical mixing methods. The higher dissolution rates and $DE_{20}$ values observed with kneaded complexes may be due to the better drug-CD inclusion during the kneading process.

**Table 1: Dissolution Parameters of Diclofenac- HPβCD-PVA Complex Systems**

| Complex System | Method of Preparation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Physical Mixing | | | Co-precipitation | | | Kneading | | |
| | $T_{50}$ (min) | $DE_{20}$ (%) | $K_1$ ($min^{-1}$) | $T_{50}$ (min) | $DE_{20}$ (%) | $K_1$ ($min^{-1}$) | $T_{50}$ (min) | $DE_{20}$ (%) | $K_1$ ($min^{-1}$) |
| Dfc-HPβCD(1:1) | >60 | 28.12 | 0.0078 | 4.1 | 57.66 | 0.0347 | 3.5 | 66.05 | 0.0519 |
| Dfc -HPβCD(1:2) | >60 | 30.79 | 0.0079 | 3.6 | 64.12 | 0.0372 | 2.9 | 77.60 | 0.077 |
| Dfc -HPβCD(1:4) | >60 | 32.02 | 0.0081 | 3.3 | 68.94 | 0.0420 | 2.9 | 79.65 | 0.111 |
| Dfc - HPβCD – PVA (1:1:0.25) | 41.25 | 28.20 | 0.0120 | 3.8 | 62.52 | 0.0819 | 2.9 | 81.30 | 0.197 |
| Dfc -HPβCD-PVA (1:1:0.5) | 38 | 31.04 | 0.0123 | 3.1 | 76.35 | 0.0921 | 2.7 | 84.41 | 0.263 |
| Dfc -HPβCD-PVA (1:2:0.25) | 17 | 39.10 | 0.0152 | 3.0 | 77.60 | 0.130 | 2.7 | 84.47 | 0.309 |
| Dfc -HPβCD-PVA (1:2:0.5) | 11.8 | 42.67 | 0.0174 | 2.8 | 82.94 | 0.222 | 2.6 | 85.81 | 0.416 |

**Table 2: Hixson – Crowell's Cube Root Dissolution Rate**
**As per Hixson-Crowell's Cube Root Model**

| Complex System | Method of Preparation | | |
|---|---|---|---|
| | Hixson – Crowell's Cube Root Dissolution Rate ($K_H$) ($mg^{1/3}.min^{-1}$) | | |
| | Physical Mixing | Solvent Evaporation | Kneading |
| Dfc-HPβCD(1:1) | 0.0067 | 0.0214 | 0.029 |
| Dfc -HPβCD(1:2) | 0.0068 | 0.0215 | 0.036 |
| Dfc -HPβCD(1:4) | 0.0069 | 0.0226 | 0.040 |
| Dfc - HPβCD –PVA (1:1:0.25) | 0.0090 | 0.033 | 0.067 |
| Dfc -HPβCD-PVA (1:1:0.5) | 0.0100 | 0.040 | 0.136 |
| Dfc -HPβCD-PVA (1:2:0.25) | 0.0119 | 0.047 | 0.147 |
| Dfc -HPβCD- PVA (1:2:0.5) | 0.0132 | 0.069 | 0.172 |

**Table 3: Enhancement of Dissolution Rate of Diclofenac by Various CD Complex Systems**

| S. No | Complex System | Method of Preparation | | |
|---|---|---|---|---|
| | | Increase in $K_1$ (No of Folds)* | | |
| | | Physical Mixing | Solvent Evaporation | Kneading |
| 1 | Dfc-HPβCD(1:1) | 1.7 | 7.5 | 11.3 |
| 2 | Dfc -HPβCD(1:2) | 1.71 | 8.0 | 16.7 |
| 3 | Dfc -HPβCD(1:4) | 1.8 | 9.1 | 24.1 |
| 4 | Dfc - HPβCD –PVA (1:1:0.25) | 2.6 | 17.8 | 42.8 |
| 5 | Dfc -HPβCD-PVA (1:1:0.5) | 2.7 | 20.0 | 57.2 |
| 6 | Dfc -HPβCD-PVA (1:2:0.25) | 3.3 | 28.3 | 67.2 |
| 7 | Dfc -HPβCD- PVA (1:2:0.5) | 3.8 | 48.2 | 90.4 |

* Ratio of $K_1$ of CD complex systems and uncomplexed drug.

Diclofenac– HPβCD (1:4) kneaded complex gave a 24.13 fold increase in the dissolution rate of diclofenac, whereas in the presence of PVA, diclofenac – HPβCD - PVA (1:1:0.25), gave a 42.6 fold increase in the dissolution rate of diclofenac. The inclusion complex diclofenac – HPβCD - PVA (1:2:0.5) gave a maximum of 90.4 fold Increase in the dissolution rate. As the concentration of the hydrophilic carrier in the inclusion complex increased, the dissolution rate of the drug also increased. The higher dissolution rates observed with diclofenac – HPβCD systems ontaining PVA is due to the enhancement of complexation cyclodextrins by the added

PVA, a hydrophilic polymer and also due to the stronger drug amorphization and better inclusion due to the combined action of CD and the hydrophilic polymer. Because of the enhancement in cyclodextrin complexation and dissolution rate by the presence of PVA, a low amount of CD can be used to get the desired dissolution rate and efficiency.

## CONCLUSION

Solid inclusion complexes of diclofenac - HPβCD in 1:1 and 1:2 ratios were prepared with and without PVA by three methods namely - physical mixing, kneading and solvent evaporation. All the complexes prepared were found to be fine and free flowing powders. The dissolution of diclofenac was rapid and higher from all the cyclodextrin inclusion complexes prepared when compared to diclofenac pure drug. The dissolution data obeyed first order kinetic model as well as Hixson-Crowell's cube root model in all the cases. All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than diclofenac indicating rapid and higher dissolution of diclofenac from its CD complexes. The $K_1$ and $DE_{20}$ values were increased as the proportion of CD in the complex systems was increased in each case. Complexes prepared by kneading method gave higher dissolution rate and $DE_{20}$ values than those prepared by co-precipitation and physical mixing methods.

Diclofenac– HPβCD (1:4) kneaded complex gave a 24.13 fold increase in the dissolution rate of diclofenac, whereas in the presence of PVA, diclofenac – HPβCD - PVA (1:1:0.25), gave a 42.6 fold increase in the dissolution rate of diclofenac. As the concentration of the hydrophilic carrier in the inclusion complex increased, the dissolution rate of the drug also increased. Because of the enhancement in cyclodextrin complexation and dissolution rate by the presence of PVA, a low amount of CD can be used to get the desired dissolution rate and efficiency.

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