Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 4, 2012

Research Article

SOLUBILITY ENHANCEMENT OF FLURBIPROFEN USING DIFFERENT SOLUBILIZATION TECHNIQUES

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Received: 23 Jan 2012, Revised and Accepted: 11 Mar 2012

ABSTRACT

In this study, the effect of β-cyclodextrin (β-CD) and co-solvents on the solubility of flurbiprofen was investigated. To know the effect of different concentration of β-CD, higher concentration (5 mM-15 mM) was preferred initially. As the solubility of flurbiprofen was not increased significantly with increase in concentration of β-CD, lower concentration range (1 mM-3 mM) was selected. From the phase solubility diagram of flurbiprofen the increase in solubility with 1 mM, 2 mM, 3 mM was found to be 7.02 times, 11.51 times, and11.41 times respectively. The drug solubility was increased linearly up to 2 mM of β-CD followed by hardly increasing the drug solubility. Later, the solubility of flurbiprofen in three different co-solvents polyethylene glycol 400 (PEG 400), propylene glycol and ethanol was determined and found to be 7.38 times, 19.43 times, and 12.34 times respectively. From the above results the optimum concentration of β-CD (2 mM) and one of the best co-solvent (propylene glycol) was selected and the effect on increase in solubility by the combination was found to be 18.85 times. It was concluded that co-solvent propylene glycol was best solubiliser among all selected.

Keywords: Flurbiprofen, β-Cyclodextrin, Co-solvents, Solubility, Propylene glycol.

INTRODUCTION

Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability[1]. Flurbiprofen is a poorly water soluble drug with a well known chiral non-steroidal antiinflammatory agent possessing analgesic and antipyretic activity. It is one of the most potent inhibitors of platelet aggregation, and it is used to treat gout, osteoarthritis, rheumatoid arthritis and sunburn[2]. However, it has poor water bioavailability due to its poor water solubility (10.45 ± 3.2µg/ml)[3]. Several attempts have reported for enhancing the solubility and bioavailability of flurbiprofen[4-7]. In the present study an attempt has been made to increase the solubility of flurbiprofen using co solvency and complexation techniques.

Co-solvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs[8-10]. Addition of a co-solvent to a formulation improves the solubility of the drug because the co-solvents reduces strong water-water interactions and thereby reduces the ability of water to squeeze out non-polar solutes Co-solvency was often considered at early stages due to its huge solubilization potential[11].

Complexation of drugs with cyclodextrin has been used to enhance aqueous solubility and drug stability[12]. Cyclodextrins are useful excipients, having the ability to interact with poorly water-soluble drugs and drug candidates, resulting in an increase in their apparent water solubility[13-15]. These are cyclic and oligosaccharides derived from starch containing six (α CD), seven (β-CD), Eight (γ-CD), nine (δ-CD) or more (α-1,4)-linked α-D-glucopyranose units, the cyclodextrin take the shape of a truncated cone or torus, rather than a perfect cylinder[14,16,17].

The primary hydroxyl group is oriented to the narrow edge of the cone at the exterior and the secondary group to the wider edge. The central cavity of the cyclodextrins molecule is linked with skeletal carbons and ethereal oxygens of the glucose residue, which gives it a relatively lipophilic character. This cavity enables cyclodextrins to complex the 'guest' drug molecules and in so doing alters the physicochemical properties of the drug[18]. The ability of cyclodextrins to form this inclusion complex with a variety of organic compounds is based on their ability to provide a hydrophobic cavity in aqueous solution for a hydrophobic guest molecule or hydrophobic moieties in the 'guest molecule'. The importance of such inclusion complexes, widely used in the pharmaceutical domain[19-21] is connected to the possibility to improve the aqueous solubility of the drug substances, or to increase the guest molecule stability, as well as the possibility to control drug release, with many potential applications in drug formulations.

MATERIALS AND METHODS

Flurbiprofen was kindly received as a gift sample from M/s Aurobindo Pharmaceuticals, Hyderabad, India. Polyethylene glycol 400, ethanol, propylene glycol, methanol and beta cyclodextrin were procured from SD Fine Chemicals Limited.

Determination of maximum wavelength of flurbiprofen

Flurbiprofen, 10 mg was dissolved in 10 ml of methanol and then the volume was made up to 100 ml with distilled water. The concentration of the resulting solution was 100 µg/ml and this stock solution was diluted with distilled water to get 2 µg/ml. The absorbance of the resulting solution was measured using UV-Visible spectrophotometer in the wavelength range of 200-400 nm.

Standard graph of flurbiprofen in distilled water

Flurbiprofen, 10 mg was accurately weighed and it was dissolved in 10 ml of methanol. The volume was made up to 100 ml with distilled water. The above solution served as stock solution. From the stock solution, dilutions are prepared giving the concentration of each solution ranging from 1-7µg/ml. Absorbance of the resulting solutions is determined at 247 nm using UV-Visible Spectrophotometer against distilled water as a blank.

Effect of β-CD on solubility of flurbiprofen

Distilled water, 7 ml was taken in 3 different test tubes and labelled as A, B, C. Flurbiprofen, 50 mg was added to all the test tubes and the 5 mM, 10 mM and 15 mM of β-CD was added to A,B,C respectively. The test tubes were kept on cyclomixer for 10 min and then the contents were transferred to 25 ml beakers and 3 ml of distilled water was added to all three test tubes, shaken, contents were transferred to the respective beakers. The beakers were kept on rotary shaker at room temperature for one day and the contents were filtered using whatman filter paper and again by using syringe filter. Then 1 ml of filtrate was taken from all the three beakers and was diluted with distilled water to 50 ml. The absorbance of diluted solutions was measured by UV-VIS spectrophotometer at 247 nm against blank solution which was prepared with same concentration of β-CD devoid of drug so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Similar procedure was followed without adding β-CD to know the aqueous solubility of flurbiprofen.

As the solubility of flurbiprofen was not increased significantly with increase in concentration of β-CD, the lower concentration range was selected and it was 1 mM, 2 mM and 3 mM. The procedure was followed similarly as described above with 1 mM, 2 mM and 3 mM of β-CD. Based on result, the optimum concentration of β-CD was selected for further study.

Effect of co-solvents on solubility

Three different co-solvents, polyethylene glycol 400, propylene glycol, ethanol were selected. Distilled water, 7 ml was taken in 3 different test tubes and labelled as A, B, C. Flurbiprofen, 50 mg was added to all the test tubes and one ml of each co-solvent was added to 3 different test tubes A, B, C respectively. The test tubes were kept on cyclomixer for 10 min and then the contents were transferred to 25 ml beakers and 2 ml of distilled water was added to all three test tubes, shaken, contents were transferred to the respective beakers. The beakers were kept on rotary shaker at room temperature for one day and the contents were filtered using whatman filter paper and again by using syringe filter. Then 1 ml of filtrate was taken from all the three beakers and was diluted with distilled water to 50 ml. The absorbance of diluted solutions was measured by UV-VIS spectrophotometer at 247 nm against blank solution which was prepared in same concentration of β-CD devoid of drug so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Based on result, one of the co-solvent was selected for further study.

Combined effect of β-cyclodextrin and co-solvents on solubility of flurbiprofen

The optimum concentration of β-CD (2 mM) and one of the best co-solvent (propylene glycol) was selected for the study.

Distilled water, 7 ml was taken in test tube. Flurbiprofen, 50 mg was added to the test tube and also one ml of propylene glycol was added. The contents were mixed using cyclomixer for 10 min, transferred to 25 ml beaker. Distilled water, 2 ml was added to test tube, shaken contents were transferred to the beaker. The beaker was kept on rotary shaker at room temperature for one day and the contents were filtered using whatman filter paper and again by using syringe filter. Then 1 ml of filtrate was taken from beaker and was diluted with distilled water to 50 ml. The absorbance of diluted solutions was measured by UV-VIS spectrophotometer at 247 nm against blank solution which was prepared in same concentration of β-CD devoid of drug so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules.

RESULTS AND DISCUSSION

Determination of maximum wavelength of flurbiprofen

The absorbance of 2 µg/ml solution of flurbiprofen was measured at 200 nm to 400 nm. The maximum wavelength of flurbiprofen was found to be 247 nm and depicted in Fig. 1.

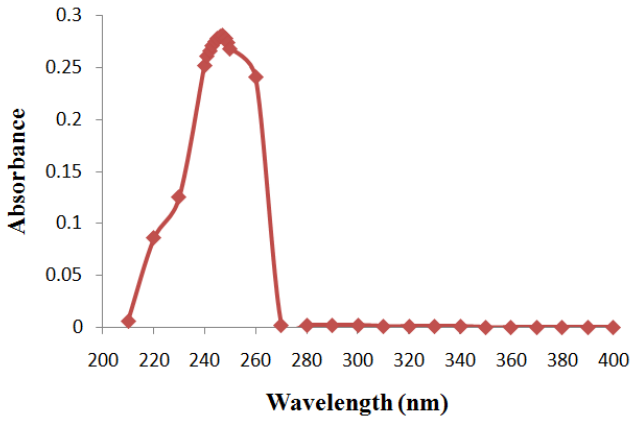

Fig. 1: UV spectrum of flurbiprofen depicting maximum wavelength.

Standard graph of flurbiprofen in distilled water

The absorbance of flurbiprofen at different concentrations was measured using UV-VIS spectrophotometer at 247 nm (Fig. 2)

Effect of β-CD on aqueous solubility of flurbiprofen

Fig. 3 shows the phase solubility diagram of flurbiprofen in β-CD obtained by plotting the changes in the drug solubility as a function of β-CD concentration. The drug solubility was increased with 5 mM of β-CD but with increase in concentration of β-CD to 10 mM and 15 mM, increased solubility was not observed.

Hence the concentration of β-CD was decreased and the effect on solubility was observed with 1 mM, 2 mM and 3 mM of β-CD. The increase in solubility with 1 mM, 2 mM and 3 mM of β-CD was found to be 7.02 times, 11.51 times and 11.14 times respectively. The drug solubility was increased linearly up to 2 mM of β-CD followed by hardly increasing the drug solubility (Fig. 4)

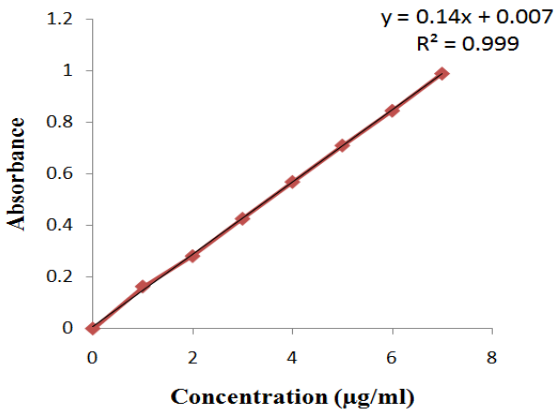

Fig. 2: Standard graph of flurbiprofen

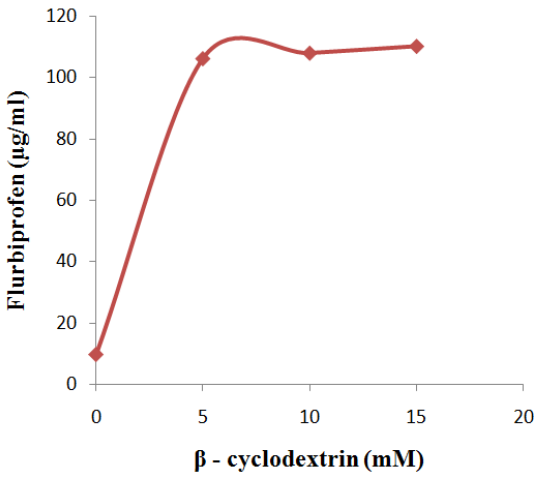

Fig. 3: Phase solubility diagram depicting the changes in the drug solubility as a function of β-CD

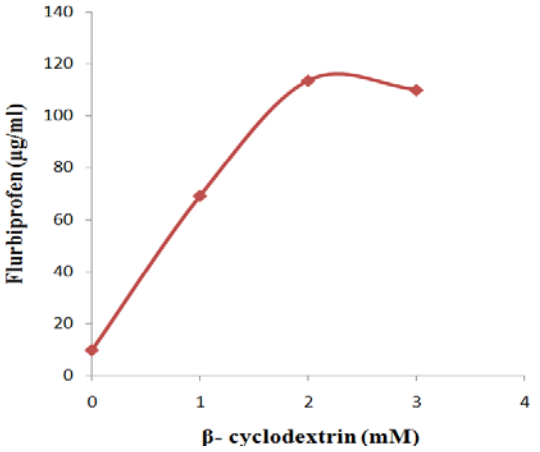

Fig. 4: Solubility curve indicating the effect of different concentration of β-CD on solubility of flurbiprofen

The solubility curve was classified as the Bs type, which revealed a formation of soluble flurbiprofen/ β-CD inclusion complex with 1:1 molar ratio stoichiometry according to Higuchi and Connors (Higuchi, Connors , 1965). The complex exhibited higher solubility than the drug molecule, but its limit was reached within the tested β-CD concentration range. Increasing the amount of available CD-molecules did not lead to a rise in drug solubility, indicating that all guest molecules have been converted into an inclusion complex with less solubility. The highest drug solubility of about 113.58 µg/ml in β-CD solution was observed with 2 mM β-CD and selected for further studies.

Effect of co-solvents on aqueous solubility of flurbiprofen

The increase in solubility with PEG 400, propylene glycol and ethanol was found to be 7.38 times,19.43 times and 12.34 times respectively and is shown in Figure 5.

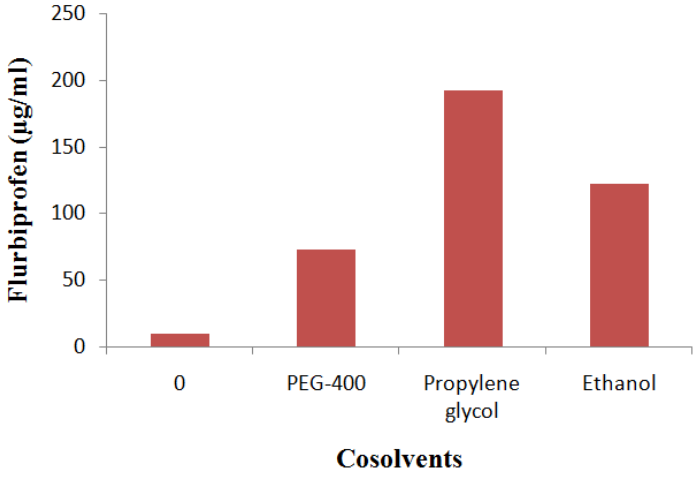

Fig. 5: Effect of different concentrations of co-solvents on solubility of flurbiprofen.

The co-solvent reduces strong water–water interactions and thereby reduces the ability of water to squeeze out non-polar solutes. Co solvency was often considered at early stages due to its huge solubilization potential. The increase in solubility with 2 mM of β-CD and 10 % v/v of propylene glycol was found to be 18.85 times. The combined effect of beta cyclodextrin and co-solvent is shown in Table 1. The combination of cyclodextrin and co-solvent didn't show synergistic effect.

Table 1: Combined effect of β-CD and Co-solvents on solubility

Co-solvent +β-CD	Absorbance	Dilution Factor	Solubility (µg/ml)
Propylene glycol + 2 mMβ-CD	0.522	50	186.08

CONCLUSION

Betacyclodextrin, 2mM, enhanced solubility of flurbiprofen by 11.51 times. Among the co-solvents used, propylene glycol exhibited highest solubility enhancement, 19.43 times more than water alone. The mixed system of drug solution containing 2mM beta cyclodextrin and 10% propylene glycol showed about 18.85 fold higher drug solubility compared to drug powder. But synergistic effect was not found. Among all the selected solvents propylene glycol was found to be the best solubiliser.

AKNOWLEDGEMENT

The authors are grateful to the management of the institute, Sultan-Ul-Uloom Educational Society, Banjarahills, Hyderabad for providing the facilities. The authors acknowledge M/s Aurobindo Pharmaceuticals, Hyderabad, India for gift sample of flurbiprofen.

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