



INDIVIDUAL AND COMBINED EFFECTS OF CYCLODEXTRIN, POLOXAMER AND PVP ON THE SOLUBILITY AND DISSOLUTION RATE OF NITRENDIPINE - A BCS CLASS II DRUG

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ABSTRACT

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Nitrendipine, an anti hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Rate limiting step for Nitrendipine oral absorption is dissolution and it requires improvement in the solubility and dissolution rate for increasing oral bioavailability. The objective of the study is to enhance the solubility and dissolution rate of Nitrendipine by cyclodextrin complexation together with Poloxamer 407 and PVP K30. The solubility of Nitrendipine was determined in β CD, individually and along with Poloxamer 407 and PVP K30. Solid inclusion complexes of Nitrendipine- β CD were prepared with and without Poloxamer 407 and PVP K30 by kneading method and were evaluated. The individual and combined effects of β CD, Poloxamer 407 and PVP K30 in enhancing the solubility, dissolution rate and dissolution efficiency of Nitrendipine were highly significant. β CD, Poloxamer 407 and PVP K30 significantly enhanced the solubility, dissolution rate and dissolution efficiency of Nitrendipine. β CD alone gave a 2.00 fold increase in the solubility of Nitrendipine. Combination of β CD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of Nitrendipine. Combination of β CD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K₁) and dissolution efficiency (DE₂₀) when compared to β CD alone. Hence a combination of β CD with Poloxamer 407 and / or PVP K30 recommended for enhancing the solubility, dissolution rate and dissolution efficiency of Nitrendipine, a BCS class II drug.

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INTRODUCTION

Nitrendipine, a widely prescribed anti-hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility¹. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability.

Several techniques² such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches complexation with cyclodextrins has gained

good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a 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 and bioavailability can be favourably affected 3,4 . Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies 5, 6 . Poloxamer 407 is a polymeric solubiliser with an amphiphilic chemical nature, which was particularly developed for solid solutions . Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (PEG). The approximate lengths of the two PEG blocks is 101 repeat units, while the approximate length of the propylene glycol block is 56 repeat units 7. Poloxamer 407 increased the solubility and enhanced the bioavailability of actives in solid solutions. Itraconazole and fenofibrate showed significant increase in the bioavailability with Poloxamer 407 8 .

The solubility and dissolution rate of etoricoxib was effectively enhanced by using Poloxamer 407 in the form of solid dispersions 9 . Poly vinyl pyrrolidone (PVP K 30) is also reported 10 to enhance the solubility and dissolution rate of poorly soluble drugs. Though cyclodextrin complexation and use of surfactants and PVP for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, very few reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation the individual main effects and combined (or interaction) effects of β cyclodextrin (β CD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of Nitrendipine, a BCS class II drug were evaluated.

EXPERIMENTAL

Materials: Nitrendipine was a gift sample from M/s. Natco Pvt. Ltd., Hyderabad. β Cyclodextrin

was gift sample from M/s. Cerestar Inc., USA. Poloxamer 407 was a gift sample from BASF, BASF, River park road, Geismar, LA70734. Methanol (Qualigens) and poly vinyl pyrrolidone (PVP K30) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Nitrendipine: An UV Spectrophotometric method based on the measurement of absorbance at 235 nm in Phosphate Buffer, pH 6.8 was used for the estimation of Nitrendipine. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 μ g/ml.

Solubility Determination: Excess drug (40 mg) was added to 15 ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28 ± 1 o C) on Rotary Flask Shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 μ disk filter. The filtered samples were diluted suitably and assayed for Nitrendipine by measuring absorbance at 235 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for three times each (n=3).

Preparation of Nitrendipine- β CD Complexes: Solid inclusion complexes of Nitrendipine in β CD with and without Poloxamer 407 - PVP K30 were prepared by kneading method. Nitrendipine, β CD, Poloxamer 407 and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of dichloromethane: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55 o C until dry. The dried mass was powdered and sieved to mesh No. 60.

Dissolution Rate Study

The dissolution rate of Nitrendipine as such and from β CD complexes prepared was studied in 900 ml Phosphate Buffer, pH 6.8 using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer

at 50 rpm. A temperature 37 ± 1 °C was maintained throughout the study. Nitrendipine or Nitrendipine- β CD complex equivalent to 40 mg of Nitrendipine was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45μ) at different intervals of time, suitable diluted and assayed for Nitrendipine at 235 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each ($n=3$).

RESULTS AND DISCUSSION

The objective of the study is to enhance the solubility and dissolution rate of Nitrendipine by cyclodextrin complexation along with Poloxamer 407 and PVP K30. The individual main effects and combined (or interaction) effects of β cyclodextrin (β CD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of Nitrendipine was also tested. The individual main effects and combined (interaction) effects of β CD, Poloxamer 407 and PVP K30 on the aqueous solubility of Nitrendipine were evaluated in alone and in combination with Poloxamer 407 and PVP K30. For this purpose, two levels of β CD (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP K30 (0, 2%) were selected in each case and the corresponding eight treatments involved were purified water (i); water containing 5 mM β CD (ii); water containing 2% Poloxamer 407 (iii); water containing 5 mM β CD and 2% Poloxamer 407 (iv); water containing 2% PVP K30 (v); water containing 5 mM β CD and 2% PVP K30 (vi); water containing 2% Poloxamer 407 and 2% PVP K30 (vii) and water containing 5 mM β CD and 2% of each of Poloxamer 407 and PVP K30 (viii). The solubility of Nitrendipine in the above mentioned fluids was determined ($n=3$) and the results are given in Table-1. The results indicated that β CD alone gave a 2.00 fold increase in the solubility of Nitrendipine. Combination of β CD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of Nitrendipine, To evaluate the individual and combined effects of β CD, Poloxamer 407 and PVP K30 on the dissolution rate of Nitrendipine, solid inclusion complexes of Nitrendipine- β CD

were prepared with and without Poloxamer 407 and PVP K30. For this purpose two levels of β CD (0 and 1:2 ratio of drug : β CD) and two levels of each of Poloxamer 407 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved were Nitrendipine pure drug (F1); Nitrendipine- β CD (1:2) inclusion binary complex (F2); Nitrendipine- Poloxamer 407 (2%) binary complex (F3); Nitrendipine- β CD (1:2) - Poloxamer 407 (2%) ternary complex (F4); Nitrendipine- PVP K30 (2%) binary complex (F5); Nitrendipine- β CD (1:2) - PVP K30 (2%) ternary complex (F6); Nitrendipine- Poloxamer 407 (2%) - PVP K30 (2%) ternary complex (F7) and Nitrendipine- β CD (1:2) - Poloxamer 407 (2%) - PVP K30 (2%) complex (F8). The CD complexes were prepared by kneading method. All the solid inclusion complexes of Nitrendipine- β CD - Poloxamer 407 /PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values ($< 1.21\%$) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of Nitrendipine alone and from β CD complexes was studied in 900 ml Phosphate Buffer, pH 6.8. The dissolution of Nitrendipine followed first order kinetics with r (correlation coefficient) above 0.983. Dissolution efficiency (DE 30) values were calculated as suggested by Khan 11 . The dissolution parameters are given in Table-2. The dissolution of Nitrendipine was rapid and higher in the case of Nitrendipine- β CD binary and ternary complex systems prepared when compared to Nitrendipine pure drug as such. The dissolution profiles are given in Fig-1. β CD alone gave a 2.67-fold increase in the dissolution rate of (K_1) of Nitrendipine. When β CD is combined with Poloxamer 407 and PVP K30 the dissolution rate (K_1) was greatly enhanced. A 6.88 and 4.11 fold increase in the dissolution rate (K_1) was observed respectively with Nitrendipine- β CD - Poloxamer 407 and Nitrendipine- β CD - PVP K30 solid inclusion complexes. Hence a combination of β CD with Poloxamer 407 and / or PVP K30 recommended for enhancing the solubility, dissolution rate and dissolution

efficiency of Nitrendipine, a BCS class II drug.

Table1. Solubility of Nitrendipine

Nitrendipine/ It's Complexes	Solubility (mg/ml)	Increase in solubility (number of folds)
Water containing NT (F1)	0.016	----
Water containing NT- β CD (1:2) (F2)	0.032	2.00
Water containing 2 % Poloxamer 407 (F3)	1.15	71.87
Water containing 5mM β CD and 2% Poloxamer 407 (F4)	0.86	53.75
Water containing 2 % PVP K30 (F5)	0.40	25.00
Water containing 5mM β CD and 2 % PVP K30 (F6)	0.54	33.75
Water containing 2 % Poloxamer 407 and 2 % PVP K30 (F7)	1.09	68.12
Water containing 5mM β CD ,2% Poloxamer 407 and 2% PVP K30 (F8)	1.37	85.62

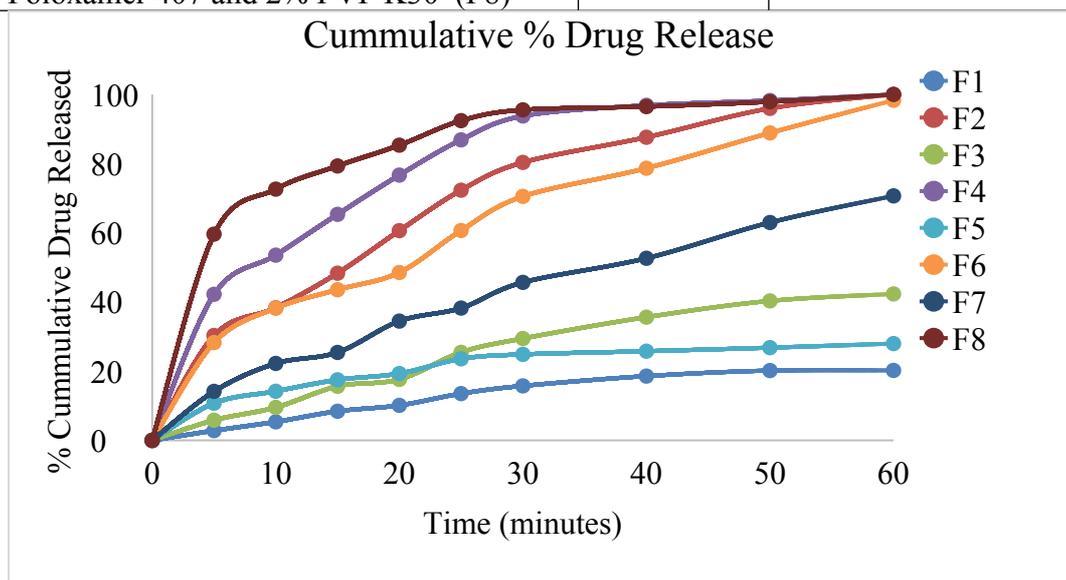


Fig.1: Dissolution Profiles of Nitrendipine– β CD Complexes Prepared by Employing β CD, Poloxamer 407 and PVP K30

Table 2: Dissolution Parameters of Nitrendipine- β CD- Poloxamer 407-PVP K30 Inclusion Complexes

EF- β CD Complex	Composition	PD ₁₀ (10%)	K ₁ (min ⁻¹)	DE ₃₀ (%)
F ₁	NT	5.36	0.005	33.40
F ₂	NT- β CD (1:2)	38.32	0.051	36.92
F ₃	NT-Poloxamer 407 (2%)	9.53	0.010	29.72
F ₄	NT- β CD (1:2) –Poloxamer 407 (2%)	53.54	0.080	44.87
F ₅	NT-PVP K30 (2%)	14.20	0.008	42.60
F ₆	NT- β CD (1:2)- PVP K30(2%)	38.23	0.041	33.02
F ₇	NT-Poloxamer 407 (2%) -PVP K30 (2%)	22.24	0.020	29.31
F ₈	NT- β CD (1:2)- Poloxamer 407 (2%)-PVP K30(2%)	72.63	0.130	49.81

NT- Nitrendipine; β CD - Cyclodextrine; PVP - Poly vinyl pyrrolidone K 30

CONCLUSIONS

β CD, Poloxamer 407 and PVP K30 significantly enhanced the solubility, dissolution rate and dissolution efficiency of Nitrendipine. β CD alone gave a 2.00 fold increase in the solubility of Nitrendipine. Combination of β CD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of Nitrendipine. β CD alone gave a 2.67 fold increase in the dissolution rate of (K₁) of Nitrendipine. A 6.88 and 4.11 fold increase in the dissolution rate (K₁) was observed respectively with Nitrendipine- β CD – Poloxamer 407 and Nitrendipine- β CD – PVP K30 solid inclusion complexes.. Combination of β CD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K₁) and dissolution efficiency (DE₂₀) when compared to β CD alone. Hence a combination of β CD with Poloxamer 407 and / or PVP K30 recommended to enhance the solubility, dissolution rate and dissolution efficiency of Nitrendipine, a BCS class II drug.

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