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Enhancement of Dissolution Rate and Bioavailability of Aceclofenac Through Complexation with β-Cyclodextrin

K.P.R. CHOWDARY* and A. SAMBASIVA RAO
University College of Pharmaceutical Sciences, Andhra University
Visakhapatnam-530 003, India
E-mail: profkprc@rediffmail.com

Aceclofenac, a widely prescribed non-steroidal antiinflammatory drug is practically insoluble in water and aqueous fluids, because of which it exhibits poor and variable dissolution rate and oral bioavailability. The objective of the study is to investigate the feasibility of using complexation with β-cyclodextrin (βCD) for enhancing the dissolution rate and bioavailability of aceclofenac. Aceclofenac-βCD inclusion complexes were prepared by kneading method and were evaluated for dissolution rate and bioavailability. The dissolution rate and bioavailability of aceclofenac were markedly enhanced by complexation with βCD. A 12.7 fold increase in the dissolution rate of aceclofenac was observed with aceclofenac-βCD (1:2) complex. Absorption rate was increased from 1.90 h^{-1} for aceclofenac to 2.76 and 4.33 h^{-1}, respectively for βCD (1:1) and (1:2) complexes. $(AUC)_{0-\infty}$ was increased from 12.60 μgh/mL for aceclofenac to 42.51 and 49.20 μgh/mL for βCD (1:1) and (1:2) complexes, respectively.

Key Words: Aceclofenac, Cyclodextrin complexation, Dissolution rate, Bioavailability.

INTRODUCTION

Aceclofenac is an orally administered non-steroidal antiinflammatory drug used in a variety of painful conditions[1,2]. Aceclofenac is practically insoluble in water and aqueous fluids. Its aqueous solubility was found to be 0.53 mg/mL. As such its oral absorption or dissolution rate is limited. The poor aqueous solubility of the drug gives rise to difficulties in the formulation of solid dosage forms and leads to poor and variable dissolution rate and oral bioavailability. Among the various methods to overcome the problems of poor aqueous solubility, cyclodextrin (CD) complexation is an industrially accepted technique. Cyclodextrins have been receiving increasing application in pharmaceutical formulations in recent years due to their approval by various regulatory agencies[3,4]. Cyclodextrins are able to form inclusion complexes with drug molecules and have been shown to

improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties[5,6]. The objective of the present work is to evaluate the feasibility of using complexation with β-cyclodextrin (βCD) for enhancing the dissolution rate and bioavailability of aceclofenac. Aceclofenac-βCD inclusion complexes were prepared by kneading method and were evaluated for dissolution rate and bioavailability.

EXPERIMENTAL

Aceclofenac (gift sample from M/s Suyaash labs, Chennai), β-cyclodextrin (gift sample from M/s Cerestar Inc., USA) and methanol (Qualigens) were used.

Preparation of aceclofenac-βCD complexes: Solid inclusion complexes of aceclofenac-βCD were prepared in 1:1 and 1:2 ratios by kneading method. Aceclofenac and βCD were triturated in a mortar with a small volume of solvent blend of water:methanol (1:3). 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.

Estimation of aceclofenac: An UV spectrophotometric method based on the measurement of absorption at 275 nm in a phosphate buffer of pH 6.8 was used for the estimation of aceclofenac. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 1-10 μg/mL. When a standard drug solution was repeatedly assayed (n = 6), the relative error and coefficient of variation were found to be 0.80 and 1.2 %, respectively. No interference by the excipients used in the study was observed.

Dissolution rate study: The dissolution rate of aceclofenac as such and from βCD complexes was studied in 900 mL of phosphate buffer of pH 6.8 using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37 ± 1 ºC was maintained throughout the study. Aceclofenac or aceclofenac-βCD complex equivalent to 50 mg of aceclofenac was used in each test. Samples of dissolution media (5 mL) were withdrawn through a filter (0.45 μ) at different intervals of time, suitably diluted and assayed for aceclofenac at 275 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were conducted in triplicate.

Bioavailability study: *in vivo* pharmacokinetic and bioavailability assessment of aceclofenac-βCD complexes in comparison to aceclofenac was carried out in rabbits. The *in vivo* study protocols were approved by institutional ethical committee.

Healthy rabbits of either sex weighing (1.5-2.5 kg) were fasted overnight. Aceclofenac and its products were administered at dose equivalent

to 10 mg/kg of aceclofenac. Each product was repeated 6 times (n = 6). The *in vivo* experiments were conducted as per a crossover RBD with a wash out period of 2 weeks in between the trails. After collecting the zero hour blood sample (blank) the product in the study was administered orally in a capsule shell with 10 mL of water. Blood samples (3 mL) were collected from marginal ear vein at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 9.0 and 12.0 h after administration. The blood samples collected were immediately centrifuged at 5000 rpm and the plasma separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay. Plasma concentration of aceclofenac in the samples was determined by a known HPLC method[7].

A 500 µL aliquot of acetonitrile was added to a 200 µL aliquot of plasma samples. After vigorous mixing, the mixture was centrifuged at 6000 rpm for 2 min. A 100 µL aliquot of the supernatent was injected directly on to the HPLC column. The mobile phase, a mixture of 5 mM sodium phosphate buffer (pH 7.2)-acetonitrile (67:33 v/v) was run at a flow rate of 1 mL/min and the column effluent was monitored at 280 nm.

RESULTS AND DISCUSSION

All the solid inclusion complexes of aceclofenac-βCD prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v) values (< 1 %) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of aceclofenac alone and from βCD complexes was studied in phosphate buffer of pH 6.8. Dissolution of aceclofenac followed first order kinetics with 'r' (correlation coefficient) above 0.91. Dissolution efficiency DE_{30} values were calculated as suggested by Khan[8]. The dissolution parameters are given in Table-1. The dissolution of aceclofenac was rapid and higher from all the solid inclusion complexes when compared to aceclofenac as such. A 7.1 and 12.7 fold increase in the dissolution rate of aceclofenac was observed with βCD 1:1 and 1:2 complexes, respectively. The dissolution efficiency (DE_{30}) of aceclofenac was increased from 34.16 % for pure drug to 82.18 and 87.89 %, respectively for βCD (1:1) and (1:2) complexes.

Pharmacokinetic parameters estimated following the oral administration of aceclofenac and its βCD complexes are given in Table-2. The elimination rate constant (K_{el}) for aceclofenac was found to be 0.173 h^{-1} and the corresponding biological half life ($t_{½}$) was found to be 4.0 h. after the oral administration of aceclofenac. The $t_{½}$ value of aceclofenac obtained in the present study is in good agreement with earlier reported[3] value of 4.8 ± 0.2 h.

The absorption rate constant (K_a) was found to be 1.90 h^{-1} following the oral administration of aceclofenac. Aceclofenac was found to be absorbed relatively slowly when given orally and the peak plasma concentration (C_{max}) of 4.10 µg/mL was observed at 2.0 h following oral administration.

TABLE-1
DISSOLUTION PARAMETERS OF ACECLOFENAC AND ITS β-CYCLODEXTRIN (βCD) COMPLEXES

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Per cent dissolved in 10 min
Aceclofenac	39	0.0214	34.16	33.41 ± 1.43
Aceclofenac-βCD (1:1) complex	3.5	0.1519	82.18	88.40 ± 1.48
Aceclofenac-βCD (1:2) complex	3.0	0.2720	87.89	97.16 ± 1.91

TABLE-2
SUMMARY OF PHARMACOKINETIC PARAMETERS ESTIMATED FOLLOWING THE ORAL ADMINISTRATION OF ACECLOFENAC AND ITS β-CYCLODEXTRIN (βCD) COMPLEXES

Formulation	C_{max} (µg/mL)	T_{max} (h)	(AUC) 0-12 h	$(AUC)_{0-\infty}$ (µgh/mL)	K_a (h^{-1})	Per cent absorbed (h)		K_{el} (h^{-1})	$t_{½}$ (h)
						0.5	1.0		
Aceclofenac	4.10	2.0	11.67	12.60	1.90	7.64	28.49	0.173	4.0
Aceclofenac-βCD (1:1) complex	11.45	1.5	41.0	42.51	2.76	53.06	81.03	0.219	3.16
Aceclofenac-βCD (1:2) complex	17.67	1.0	47.80	49.20	4.33	39.48	98.68	0.230	3.0

All the pharmacokinetic parameters of absorption (Table-2) namely K_a, C_{max}, T_{max}, per cent absorbed to various times and AUC indicated rapid absorption and higher bioavailability of aceclofenac when administered as βCD complexes. The absorption rate constant (K_a) was found to be 2.76 and 4.33 h^{-1}, respectively with aceclofenac-βCD (1:1) and (1:2) complexes. Whereas in the case of aceclofenac, K_a was only 1.90 h^{-1}.

$(AUC)_{0-\infty}$ (extent of absorption) was also much higher in the case of βCD complexes when compared to aceclofenac. $(AUC)_{0-\infty}$ was increased from 12.60 µgh/mL for aceclofenac to 42.51 and 49.20 µgh/mL for βCD (1:1) and (1:2) complexes, respectively.

Conclusion

Dissolution rate and dissolution efficiency of aceclofenac were markedly enhanced by complexation with β-cyclodextrin (βCD). A 12.7 fold increase in the dissolution rate of aceclofenac was observed with aceclofenac-βCD (1:2) complex.

Pharmacokinetic studies indicated rapid and higher oral absorption of aceclofenac when administered as βCD complexes. Absorption rate (K_a) and bioavailability (AUC) were markedly enhanced by βCD complexation.

REFERENCES

1. R.N. Brogden and L.R. Wiseman, *Drugs*, **52**, 113 (1996).
2. M. Grau, J.L. Grauch, A. Montero, A. Felipe and S. Julia, *Arzneim-Forsch*, **41**, 1265 (1991).
3. D.O. Thompson, *Crit. Rev. Ther. Drug Carrier Syst.*, **14**, 1 (1997).
4. A.R. Hedges, *Chem. Rev.*, **98**, 2035 (1998).
5. K.H. Fromming and J. Szejtli, Cyclodextrins in Pharmacy, Kluwer Academic Publications, Dordrecht, p. 20 (1994).
6. D. Duchene and D. Wouessidjewe, in ed.: S. Dumitriu, Polysaccharides in Medical Applications, Marcel Dekker, New York, p. 575 (1996).
7. Y.G. Kin, Y.J. Lee and H.J. Kim, *Int. J. Clin. Pharmacol. Ther.*, **39**, 83 (2001).
8. K.A. Khan, *J. Pharm. Pharmacol.*, **27**, 48 (1975).

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