SHORT COMMUNICATIONS

Effect of Cyclodextrins of the Stability of New Antimalarial Compound N^1-3'-Acetyl-4',5'-Dihydro-2'Furanyl-N^4-(6-Methoxy,8-Quinolinyl)-1,4-Pentane Diamine#

A.K. DWIVEDI*, D. KULKARNI, M. KHANNA, AND S. SINGH
Division of Pharmaceutics, C.D.R.I., Lucknow-226 001

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The compound N^1-3'-acetyl-4'5'-dihydro-2'-furanyl-N^4-(6-methoxy,8-quinolinyl)-1,4-pentane diamine [80/53] (I), an anti-relapse antimalarial compound, is now under phase II clinical trials. It was observed that the compound is less stable in acidic medium. Therefore, the present investigation was taken up to study the effect of β-and γ-cyclodextrins on the stability of the above compound. The solution of I as well as its cyclodextrin complexes were prepared in acetate buffers of different pH. The order of reaction and degradation rate constant at 30±2° were computed by least square linear regression. The I : β cyclodextrin (1:2) complex showed the best stability of I.

8-Aminoquinoline derivatives are known to have tissue schizonticidal (causal prophylactic and radical curative) as well as gametocidal activity against malaria. Primaquine is in clinical use as an anti-relapse drug against *Plasmodium vivax*. It has several adverse side effects, such as methemoglobinemia and cyanosis, hemolytic anemia in G-6-PD deficient individuals, hepatotoxicity, gastrointestinal distress, nausea, vomiting, anorexia and headache. A number of analogues of primaquine were synthesized and evaluated, either by quinoline ring substitution or by side chain modification, in search for compounds that would be more effective or less toxic[1,2]. Compound 80/53, N^1-3'-(acetyl-4'5'-dihydro-2'-furanyl)-N-^{4}(6-methoxy-8-quinolynyl)-1,4-pentanediamine (Fig. 1) is a potent anti-malarial agent, synthesized as a prodrug of primaquine[3,4].

The compound has been evaluated for anti-relapse activity against sporozoite-induced *Plasmodium Cynomolgi* infection in the rhesus monkey. It is safer than primaquine and causes only one third as much methemoglobinemia. It is also safe in subacute toxicity studies in rats and rhesus monkeys[5]. Currently it is under phase II clinical trials. The compound undergoes hydrolysis which is catalyzed by acidic conditions. UV scanning depicts that absorbance of the drug solution decreases at wavelength 302[6] nm but remains constant at 269 nm[7,8]. In acidic medium, the compound gets converted into primaquine[9]. Optimum stability is found to be between pH 7-8. The objective of this paper is to study the effect of β-and γ-cyclodextrins on the stability of N^1-3'-(acetyl'4',5'-dihydro-2'-furanyl)-N^4-(6-methoxy-8-quinolynyl)-1,4-pentanediamine in water solution.

All the chemicals and reagents used were of Anal R grade. The cyclodextrins were generous gifts from Department of Pharmaceutical Sciences, Aston University Birmingham, UK. The UV spectra were recorded using a Shimadzu 260 UV visible spectrophotometer (Japan) and DSC spectra were recorded on a Mettler TA 4000 system.

The cyclodextrin complexes were prepared by stirring, mixed solutions of equal volumes of 80/53 (0.005 M) in isopropanol and respective cyclodextrin (0.005 M) or (0.01 M) in water, for two hours. The resulting solutions were spray dried using Buchi mini spray drier and the complex formation was checked by recording its DSC spectra.

Five milligrams of 80/53 was dissolved in 10 ml of 0.1 M methanolic NaOH to prepare a stock solution. NaOH

*For Correspondence

Table I - Kinetics data of 80/53 complexes

Compound	k_{obs} x10^{-2}				T (50%)(in min.)			
	pH-4	pH-5	pH-6	pH-7	pH-4	pH-5	pH-6	pH-7
80/53 (j_o)	8.87	5.20	0.524	0.485	7.81	13.32	132.3	143.0
80/53:β-CD (1:1)	0.55	0.35	0.269	0.266	126.0	198.7	257.45	260.5
80/53:β-CD (1:2)	0.25	0.225	0.230	0.224	282.1	299.0	308.6	309.1
80/53:γ-CD (1:1)	4.61	0.907	0.568	0.278	15.04	76.1	122.08	249.3
80/53:γ-CD (1:2)	0.47	0.435	0.364	0.216	146.9	159.3	190.50	320.3

First order kinetics of 80/53 and its cyclodextrin complexes.

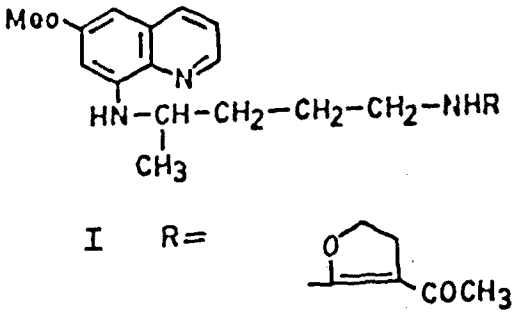

Fig. 1 : Structure of compound 80/53

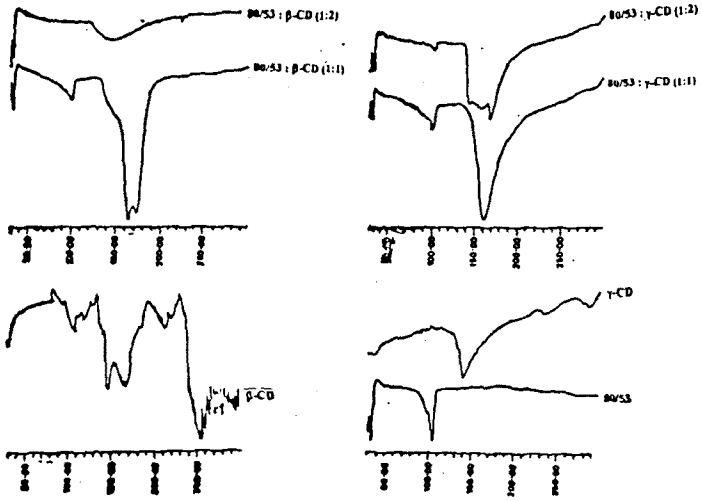

Fig. 2 : DSC spectra of 80/53 : β-CD (1:1),80/53 : β-CD (1:2), 80/53 : γ-CD (1:1), 80/53 : γ-CD (1:2), 80/53, β-CD and γ-CD.

was used to prevant degradation of 80/53 in methanolic solution. The solutions of different pH range 4 to 7 were prepared by adjusting the pH of 0.05 M acetate buffer by 0.01 N HCl/0.02 N NaOH. The ionic strength was kept constant by using 0.02 N KCl solution. The solution for stability studies of 80/53 were prepared by adding an appropriate quantity of the stock solution of 80/53 in acetate buffers to make 100 µg/ml 80/53 solution. The solutions of the cyclodextrin complexes, equivalent to 100 µg/ml of 80/53, were prepared by dissolving the respective complex in the buffer solutions. The degradation of 80/53 studied by monitoring the absorbance at 302 nm on U.V. spectrophotometer[6]. The per cent concentration of remaining of 80/53 was calculated from the calibration curves plotted at each pH.

The DSC spectras of the compound 80/53 and its cyclodextrin complexes are given in figure 2 which indicated that the complexation took place in the case of I: β–cyclodextrin (1:2). It was reported earlier[9] that this compound followed the first order degradation kinetics. The first order kinetic parameters-the observed rate constant[11] [k_{obs}] and the half life of 80/53 at different pH solutions was calculated by using the LINREG programme[10] (Table 1). The data showed that the observed rate of degradation of I decreases by increasing pH from 4 to 7. The β-and γ-cyclodextrins both stabilized 80/53 and the compound was more stable in 80/53:β-cyclodextrin (1:2) than 80/53:β-cyclodextrin (1:1) complex. It was also evident

from the above table that the compound was more stable in presence of two moles of β-cyclodextrin than the same amount of γ-cyclodextrin. The half life of 80/53 was almost constant in 80/53:β-CD (1:2) complex. It was found to be about 300 min at all the pH studied as compared to 80/53 itself which varied from 8 minutes at pH 4 to about 143 minutes at pH 7. Thus it can be concluded that β-cyclodextrin increases the stability of 80/53 in solution in 1:2 (80/53:βcyclodextrin) molar ratio.

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REFERENCES

1. Dutta, G.P., Puri, S.K., Bhaduri A.P. and Seth, M., **Am. J. Trop. Med. Hyg.,** 1989, 41, 635.
2. Puri, S.K., Srivastava, R., Pandey, V.C., Sethi, N. and Dutta, G.P., **Am. J. Trop. Med. Hyg.,** 1989, 41, 638.
3. Bhat, B., Seth, M., Bhaduri, A.P., Raina, R., Pal, N.L., Chandra, S. and Sen, A.B., Indian Patent No. 15811 (1983), **Chem. Abs.** 1987, 107, 776490.
4. Bhat, B. and Bhaduri, A.P., **Indian J. Chem.,** 1985, 24B 419.
5. Sinha N. and Sethi N.,In; S. Kumar, A.K. Sen, G.P. Dutta, R.N. Sharma Eds. Tropical diseases molecular biology control and strategies, Publication & Information directorate, New Delhi, India. 1994, 262.
6. Seth, R.K., Dwivedi, A.K., Singh, C., Chaudhary, M. and Sarin, J.P.S., **The Eastern Pharmacist,** 1989, 32, 123.
7. Dwivedi, A.K., Khanna, M., Pal R. and Singh, S., **Indian J. Pharm. Sci.,** 1997, 59, 321.
8. Jain G.K. and Singh, S., **Indian J. Pharm. Sci.,** 1990, 52, 195.
9. Monif, T., Prakash, P, Dwivedi, A.K., Kulkarni, D. and Sarin, J.P.S., **Indian J. Pharm. Sci.,** 1993, 55, 196.
10. Irwin, W.J. Kinetics of Drug Decomposition, Basic computer solutions, Elsevier 1990, 2.
11. Loftsson, T. and Brewster, M.E., **J. Pharm. Sci.** 1996, 85, 1022.

Determination of Some Sulpha Drugs With Potassium Ditelluratocuprate (III) in Alkaline Medium

D. SINGH*, KALPANA SINGH AND B.B. PRASAD
Analytical Division, Chemistry Department, Faculty of Science,
Banaras Hindu University, Varanasi-221 005

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A simple and convenient titrimetric method for the determination of sulpha drugs in pure form, at milligram level, is developed using potassium ditelluratocuprate (III) in alkaline medium. The response of the titration is observed to be precisive between 1-10 mg drug sample within ±0.5%.

Sulpha drugs are widely used in the treatment of infections[1], especially for patients intolerant to antibiotics. Therefore a rapid, accurate and an economic method for their determination is essential. Determination of sulpha drugs is reported by titrating as acids and bases[2-4], through bromination[5,6] and chlorination[7]. Estimation of certain sulpha drugs, in mg quantities with the use of N-bromosuccinimide has been reported[8]. Where as, the halogenation method needs drastic reaction conditions, the use of N-bromosuccinimide in the other method is cumbersome owing to its instability at room temperature. Though the nitrite titration method[9,10] has been used for the determination of sulpha drugs, the diazotization may get influenced by several factors including the unstable behaviour of diazo salts and nitrous acid involved. Determination of certain sulpha drugs with ammonium hexanitratocerate (IV)[11] in nitric acid medium has been reported. A new method has been proposed for the determination of sulpha drugs through conversion into

*For Correspondence