SHORT COMMUNICATIONS

Development of stable formulation of Picroliv, a new hepatoprotective agent

A. K. DWIVEDI*, D. KULKARNI AND S. SINGH
Divn. of Pharmaceutics, Central Drugs Research Institute, Lucknow-226 001.

Received 13th July, 1994.

The effect of various antioxidants and alkalinizer on the chemical stability of Picroliv in the granule (Prepared by slugging) formulations at various temperatures was investigated. Picroside I, one of the major active compounds, was chosen as the marker. The order of reaction, degradation rate constant were computed by least square regression analysis.

PICROLIV[1], is a new hepatoprotective agent, which is obtained from the ethanolic extract of the roots of **Picrorrhiza kurroa**. This is now in phase II clinical trials at C.D.R.I. Lucknow. Picroside 1 (6'-0-cinnamoy1 catalpol)[2,3,4] is one of the major active constitute of Picroliv. In our previous studies it was found that the shelf-life of picroside 1 in picroliv is about five months[5]. The factors responsible for its decomposition are moisture and the oxidation of the active constituents.

On the basis of these findings four granule formulations of Picroliv were prepared. The first formulation contained only Picroliv, to the second formulation calcium carbonate was added as alkaliniser. To the third and fourth formulations antioxidants were added which was potassium metabisulphite and ascorbic acid respectively. The chemical stability of the drug in these formulations at high temperature was investigated to provide basic information for pharmaceutical design of suitable dosage form of Picroliv.

All the chemicals and reagents used were of AR grade. The HPLC of the samples was carried out on Perkin Elmer 250 binary pump (Perkin Elmer, U.S. A);in Rheodyne model 7125 injector with 20@14 μL loop (Berkeley, California, U.S.A.) and Perkin Elmer 235 diode array detector (Perkin Elmer, U.S. A.). Separation was achieved on a 5 cm x 0.4 cm ID, C-18 5 μm Particle size cartridge column (E. Merck, India Ltd.) preceded by a 2 μm precolumn (Perkin Elmer, U.S.A.). The mobile phase consisted of acetonitrile water 15:85 and detection wave length used was 280 mm.

Picroliv in formulation 1, alongwith calcium carbonate (11.0%w/w of total granulation mixture for formulation II, potassium metabisulphate (0.16% w/w) for formulation III and ascorbic acid (1.68% w/w) for formulation IV were weighed and mixed thoroughly using microcrystalline cellulose as filler and starch as granulating agent. The granule were prepared by the dry granulation method of slugging. Slugs of 300 mg were prepared using magnesium stearate as lubricant on a single punch Korsch tablett-ing machine and subjected to particle size reduction using mortar and pestle. Granules were sieved through 40-60 mesh size.

100 mg of the granules of each formulation were stored at 40°, 50° and 60° in sealed grass vials. Samples were withdrawn at regular time intervals, analysed by HPLC[6] and the amount of Picroside I

Table -1

Temperature (°C)	Formulation I		Formulation II		Formulation III		Formulation IV	
	Rate Constant (day^{-1})	t90% (days)	Rate Constant (day^{-1})	t90% (days)	Rate Constant (day^{-1})	t90% (days)	Rate Constant (day^{-1})	t90% (days)
40°	1.908×10^{-3}	55.2	2.527×10^{-3}	41.7	1.7726×10^{-3}	61.20	8.819×10^{-4}	119.5
50°	4.9556×10^{-3}	21.3	3.1375×10^{-3}	33.6	2.98×10^{-3}	35.4	2.086×10^{-3}	50.5
60°	6.262×10^{-3}	16.8	5.0281×10^{-3}	20.95	6.5217×10^{-3}	16.16	4.01×10^{-3}	26.3
25°	1.259×10^{-3}	83.40	1.205×10^{-3}	87.13	4.898×10^{-4}	214	2.512×10^{-4}	418

(CALCULATED)

was determined by calculating the concentration from the peak height of Picroside I (an active constituent) after an appropriate dilution.

The degradation curves of the granules indicated that the drug deteriorates according to first order kinetics[7]. The degradation rate constants (k) at different temperatures were calculated[8].

The values of the degradation rate constants at 40°, 50°, 60° are given in **Table 1**. The k values at 25° were determined from the Arrhenius plot. The shelf life (t90%) was calculated by using the formula $t90\% = \frac{0.105}{k}$ which are reported in Table 1.

The results indicate that the formulation prepared by using ascorbic acid as an antioxidant is the best of all, followed by that prepared using potassium metabisulphite as an antioxidant. Addition of calcium carbonate (Formulation II) did not have much effect on stability, its shelf life being the same as the Formulation I prepared as control using Picroliv alone.

The above study showed that the auto-oxidation of Picroliv is responsible for the decomposition of Picroside I which can be prevented by the addition of the antioxidants like ascorbic acid in the formulation design. Hence, the granules prepared by using ascorbic acid can be used for preparation of tablets or for filling in capsules.

ACKNOWLEDGMENTS

The authors are thankful to director, C.D.R.I. Lucknow for providing fellowship to one of them (D.K.) and Mrs. M. Chaudhary for technical assistance.

REFERENCES

1. B.S. Aswal, R. Chandra, S. K. Chatterjee, B. N. Dhawan, Y. Dwivedi, N. K. Garg, Poonam Jain, N. K. Kapoor, D. K. Kulshreshtha, B. N. Mehrotra, G. K. Patnaik, R. Rastogi, J. P. S. Sarin, K.C. Saxena, S. C. Sharma, S. K. Sharma, Binduja Shukla and P. K. S. Visen., Ind. Patent File No. 450/DEL/90.

2. Kitagawa, I., Hino, K., Nishimura, T., Kukai, E., Yosioka I., Inouye, K., and Yoshida,T., **Tetrahedron lett.** 1969, 43, 3837.

3. Singh, B., and Rastogi, R. P., **Ind. J. chem.** 1972, 10, 29.

4. Kloss, Peter, Schwobe, Willmaro, **Ger Oftea** 1973, 2,203,884.

5. **C.D.R.I. annual report** 1990-91, 64.

6. Dwivedi A. K., Chaudhary M., Seth R.K., and Sarin J. P.S., **Ind. J. Pharm. Sci.** 1989, 51 (6), 274.

7. Irwin W.J., kinetics of Drug Decomposition basic computer solutions. E L sevier 2 (1990).

8. Martin A. N., Swarbrick J., and Commarata A., Physical Pharmacy, 2nd ed., Lea and Febiger, Philadelphia, 1969, p. 359.