DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(7), 1267-1274 (1994)

DISSOLUTION SYSTEM FOR NIFEDIPINE SUSTAINED RELEASE FORMULATIONS

R.S. CHAUDHARY * , S.S. GANGWAL , V.K. GUPTA , Y. N. SHAH , K.C. JINDAL , S. KHANNA

LUPIN LABORATORIES LIMITED, MIDC, CHIKALTHANA, AURANGABAD, INDIA

ABSTRACT

An in-vitro system for evaluating Nifedipine sustained release formulations has been developed. Two systems were evaluated to simulate sink conditions and correlate the system with flow through dissolution system in mechanism. For the purpose of evaluation two commercial brands were studied. The acidic biphasic system was found to be good for in-vitro dissolution rate evaluation of sustained release nifedipine tablets. It can be successfully utilized for routine quality control work.

---

* To whom Inquiries should be directed.

INTRODUCTION

Nifedipine, one of the most potent calcium antagonists in clinical use, was introduced for the treatment of ischemic heart disease[1] and has shown anti-hypertensive effects[2]. The absorption of nifedipine, however, is inferior when administered orally in a solid dosage form because of its poor water solubility. Nifedipine is practically insoluble in water[3].

The purpose of the present study was to examine the relationship between the release rates of nifedipine from the sustained release formulations available. Nifedipine being a poorly water soluble drug its absorption is dependent on dissolution rate. The dissolution process has a rate determining effect on the absorption process [4].

It would be ideal if a relatively simple and inexpensive apparatus and methodology could be used to determine the dissolution rate of the product. An acidic biphasic dissolution system using simulated gastric fluid and 1-octanol system is suggested for insoluble drugs to simulate flow through cell conditions in literature[5], which was evaluated for nifedipine sustained release formulations.

MATERIALS AND METHODS

MATERIALS

The USP XXII dissolution apparatus type 2 was used throughout the experiment with a modification of

paddle. An additional paddle was introduced at the interface in case of biphasic system. U.V. spectrophotometer Lambda 15 of Perkin Elmer was used for determination of Nifedipine content. Nifedipine reference standard obtained from USP was used for standard solutions.

METHOD

The ultraviolet spectra of Nifedipine were taken with a Perkin-Elmer UV-spectrophotometer Lambda 15 at a concentration of 1 mg in 100 ml Octanol,and 1 mg in 100 ml 0.54 % Sodium Lauryl Sulphate solution.The substance showed absorption maxima at 206,236 & 340nm in Octanol and Sodium Lauryl Sulphate solutions. Both solutions were exposed to light for 60 minutes & again scan was taken. It was oberved that absorption at 340 nm is least affected as compared to other absorption maxima.

On this basis 340 nm was selected for determining Nifedipine concentration in dissolution fluid. Linearity was determined in Octanol (0 - 100 ppm) and in 0.54% Sodium Lauryl Sulphate Solution,(0 - 25 ppm) which follow Beer's Law .

DISSOLUTION SYSTEM - I

The USP XXII apparatus 2 was used. Study was carried out in 900 ml of 0.54 % Sodium Lauryl Sulphate Solution in distilled water. The 37°C temperature was maintained throughout the study. The paddles were rotated at 70 rpm , 5ml samples were removed at every

hour upto 8 hours. The samples were analysed at 340 nm after filtration.

DISSOLUTION SYSTEM - II

The USP XXII appratus 2 with modification was used. Study was carried out in acidic biphasic system consisting of 500 ml simulated Gastric fluid and 400 ml Octanol. An additional paddle was introduced on the same shaft to stir the interface of the liquid. The dosage forms were added when the temperature of the medium reached 37°C. The paddles were rotated at 70 rpm , 5 ml samples were removed at every hour upto 8 hours. The samples were analysed at 340 nm after filtration.

RESULTS AND DISCUSSION

For dissolution studies an automatic system for dissolution of slightly soluble drug substance is described where aqueous dissolution medium is pumped through a flow-through cell of variable design. Because of the poor substance wettability flow-through cell with stirrer have been recomended for Nifedipine[6]. Dissolution rate data of sustained release dosage forms are given in Table -I. The dissolution profile of both marketed products is much higher than the reported specifications for sustained release nifidipine formulations by Bayer, Germany for their product Adalat SR (40-70% reaches in 2 hours and minimum 65% in 6 hours) [7].

TABLE-I:DISSOLUTION RATE PROFILE OF TWO COMMERCIAL BRANDS OF NIFEDIPINE SUSTAINED RELEASE FORMULATIONS

Time	Dissolution System -I		Dissolution System -II	
Hours	Product-A (%Drug Rel)	Product-B (%Drug Rel)	Product-A (%Drug Rel)	Product-B (%Drug Rel)
0.5	10.28±1.16	13.30±1.18	5.37±0.85	3.51±0.88
1.0	35.65±2.49	45.72±2.19	13.16±1.73	17.03±3.31
2.0	42.64±3.24	61.81±3.67	25.33±2.60	57.06±3.47
3.0	46.96±2.85	68.46±5.82	32.11±3.10	78.21±3.28
4.0	49.89±3.60	70.47±4.64	37.54±3.30	85.87±2.03
5.0	52.71±3.80	76.17±4.18	42.39±3.80	89.29±2.30
6.0	53.98±4.10	77.98±5.27	46.60±4.10	100.5±5.30
7.0	55.66±4.13	77.04±3.65	50.64±4.30	100.6±3.20
8.0	58.59±3.90	85.71±3.84	53.35±4.50	100.8±2.00

The Dissolution Release profile in system I shows no correlation with the specification given by Bayer , where as in case of system II one product complies with Adalat SR specifications of dissolution rate profile. The variations in the dissolution rates of the studied commercial brands of Nifedipine Sustained Release tablets could be due to many variables. Some of these variables could be, type of diluent[8], binder[9], lubricant [10] and other adjuants [11] ,

the method of incorporation of the ingredients,the compressional force and the speed of compression are the factors leading to the variation in dissolution rate.

The dissolution system II is giving consistant reproducible results and could be correlated well with the flow through type of appratus because of the mechanism involved is similar in both the cases. In system II as the drug is getting released into water phase it is being partitioned between water/octanol phase and the drug migrates to the octanol phase without affecting the tablets. This leads to a situation where at any point of time, saturation point it not reached in water phase because of the high distribution coefficient of Nifedipine between 1-octanol/water which is of about 10,000 : 1.

In the dissolution system I results are not reproducible and variation observed is high, another disadvantage is solubilisation of other excipients in the dissolution fluid because of the surfactant. The mechanism involved in this system is to prevent the saturation stage by solubilization of the nifedipine released. This is not a true simulation of flow through system. The commercial brand under investigation were also subjected to content uniformity test as per USP monograph. Results show that both brands complies with the test. All the experiments were conducted in darkroom with a red light arrangement as nifedipine is sensitive to light.

CONCLUSION

The present work shows that dissolution system II is good enough to evaluate sustained release Nifedipine for in-vitro dissolution rate profile. It could be concluded from the results that system is suitable for day to day invitro evaluation in absence of flow through type of dissolution apparatus. It could be easily applied in USP XXII type 2 apparatus with minor modification of shaft of the paddle. This system can also be utilised for plain Nifedipine tablets.

REFERENCES

1. B.W.Johansson, Acta. Pharmacol. Toxicol., 43, Suppl. I, 45-50 (1987).
2. O.Lederballe Pederson, E. Mikkelsen, Eur. J. Clin. Pharmcol. 14, 375-381 (1987).
3. USP XXII, Mack Publishing company, Easton,1990.
4. J.A.Hersey, "Methods Available for the determination of in-vitro Dissolution Rate," Manuf. Chem. Aersol. News, Vol 40, 32-35,(1969).
5. J.A. Stead, et. al., " Ibuprofen Tablets : Dissolution & Bioavaibility studies," Int. J. Pharm., 14, 59-772, Mar (1983).
6. J. Milovac, Z. Kopitar, M. Zorz, F.D. Culing, Farm. Vestn.(Ljubljana, Yogoslavia), 36, 21 (1985).
7. Adalat, Kapseln, Tabletten, Parenteralia, Bayer Leverkusen, West Germany, February 1986, p.90.
8. E. Marlowe, R.F. Shangraw, J. Pharm. Sci., 56, 498,(1987)

9. J.T. Jacop, E.M. Plein, J.Pharm.Sci. 57, 802, (1962).

10. G. Levy, R.H. Gumtow, J. Pharm. Sci.,52, 1139, (1963).

11. S. Sovlang, P. Finholt, Medd. Norsk. Farm. Selsk., 31, 101, (1969).