Int. J. Chem. Sci.: 9(2), 2011, 924-928
ISSN 0972-768X
www.sadgurupublications.com

PHARMACOKINETIC EVALUATION OF STARCH ACETATE MICROCAPSULES OF NIFEDIPINE FOR *IN VIVO* CONTROLLED RELEASE

K. P. R. CHOWDARY[*] and G. V. RADHA[a]

University College of Pharmaceutical Sciences, Andhra University, VISAKHAPATNAM (A.P.) INDIA
[a]GITAM Institute of Pharmacy, GITAM University, Rushikonda, VISAKHAPATNAM (A.P.) INDIA

ABSTRACT

Nifedipine, an effective and widely prescribed antianginal drug requires controlled release formulation owing to its short biological half life 2.5 h and its rapid elimination. Starch acetate coated microcapsules of nifedipine exhibited good controlled release characteristics *in vitro* by providing slow release of nifedipine over 24 h. The objective of present study is to evaluate the pharmacokinetics of starch acetate microcapsules of nifedipine in comparison to nifedipine soft capsules (as reference standard) with a view to evaluate the release retarding and rate controlling efficiency of starch acetate *in vivo*. Nifedipine absorption was rapid with a rate constant (K_a) of 2.05 h^{-1} in case of soft capsules, whereas with starch acetate microcapsules, the absorption was slow over longer periods of time with a K_a of 0.177 h^{-1}. MRT was increased from 2.5 h for soft capsules to 9.6 h with starch acetate microcapsules indicating longer stay of drug in the body, when administered as starch acetate microcapsules. The relative bioavailability of nifedipine from starch acetate microcapsules was (140.94%), when compared to soft capsules (100%). Starch acetate microcapsules exhibited good release retarding and rate controlling effect *in vivo*. Nifedipine was released and absorbed slowly over longer periods of time *in vivo* resulting in the maintainance of serum concentrations within a narrow range over longer periods of time.

Key words: Starch acetate, Microcapsules, Nifedipine, Controlled release.

INTRODUCTION

Nifedipine is an effective and widely prescribed antianginal drug. It requires controlled release owing to its short biological half life of 2.5 h. A few sustained release formulations of nifedipine are available commercially. Starch acetate coated microcapsules of nifedipine exhibited[1] good controlled release characteristics *in vitro* by providing slow release of nifedipine over 24 h. The objective of present study is to evaluate the pharmacokinetics of starch acetate microcapsules of nifedipine in comparison to nifedipine

[*]Author for correspondence; E-mail: prof.kprchowdary@rediffmail.com

soft capsules (as reference standard) with a view to evaluate the release retarding and rate controlling efficiency of starch acetate *in vivo*.

EXPERIMENTAL

Materials and methods

Starch acetate coated micro capsules containing 94.4% nifedipine (size: 715 microns, 20/30 mesh) were prepared in the laboratory. Nifedipine soft capsules were procured from market. Acetonitrile (HPLC grade), water (HPLC grade) and methanol (HPLC grade) were procured from commercial sources. All other materials used were pharmacopoeial grade.

In vivo study protocol

The pharmacokinetic study was conducted as a crossover RBD in healthy rabbits of either sex (n = 6) with a wash out period of one month. The *in vivo* protocols were approved by Institutional Animals Ethics Committee (Regd. No 516/01/a/CPCSEA).

Healthy rabbits of either sex, weighing 1.5-2.5 Kg were fasted overnight. The products were administered at a dose of 0.4 mg per kg of nifedipine. After collecting the 'zero' hour blood sample (blank), the product in the study was administered orally with 10 mL of water. Blood samples (3 mL) were collected from marginal ear vein at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h after administration. Blood samples collected were centrifuged at 10,000 rpm for 10 min and the serum separated was collected into dry tubes and samples were stored under refrigerated conditions prior to assay for nifedipine. A known HPLC method[2] was used for estimation of nifedipine concentration in serum samples.

HPLC system (make: M/s. Shimadzu Corporation, Japan) consisting of UV-Visible detector (Shimadzu, model : SPD-10 AVP), C-18 column (Phenomenex, DESC : Gemini 5 µ C18110A, Size: 250 X 4.6 mm, S/No. 288063-23), 2 pumps (Model : LC – 10 ATVP) and a micro syringe of capacity 25 µL (Model : Microliter® # 702, Mfd by : M/s. Hamilton) was used. The mobile phase consists of a mixture of water : acetonitrile : methanol (37.5 : 37.5 : 25). The mobile phase was filtered through 0.45 µ membrane filter before use and run at a flow rate of 1 mL/min. The column effluent was monitored at 238 nm.

Procedure

Methanol (100 µL) and acetonitrile (1 mL) were added to 0.5 mL of serum and agitated for 5 mins with a cyclomixer. After centrifugation at 5000 rpm for 5 mins, 1 mL of

supernatant was transferred to a stoppered tube and then 5 mL of chloroform-acetone mixture (2 : 1 v/v) was added. The mixture was shaken for 15 min. and centrifuged at 5000 rpm for 5 min.; then 4.5 mL of the organic layer was transferred to a boiling tube and evaporated to dryness at 40°C under reduced pressure. The residue was dissolved in 0.5 mL of the mobile phase consisting of water : acetonitrile: methanol (37.5 : 37.5 : 25). Subsequently, 20 µL was injected into the column for HPLC analysis. A calibration curve was constructed initially by analyzing serum samples containing known amounts of nifedipine.

Data analysis

From the time vs. serum concentration data, various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), area under the curve (AUC), elimination rate constant, (K_{el}), biological half-life ($t_{1/2}$), percent absorbed to various times, relative bioavilability, absorption rate constant (Ka) and mean residence time (MRT) were calculated as per known standard methods[3,4].

RESULTS AND DISCUSSION

The serum concentrations of nifedipine following the oral administration of nifedipine soft capsules and controlled release microcapsules in rabbits (n = 6) are shown in Fig. 1. The summary of pharmacokinetic parameters estimated is given in Table 1.

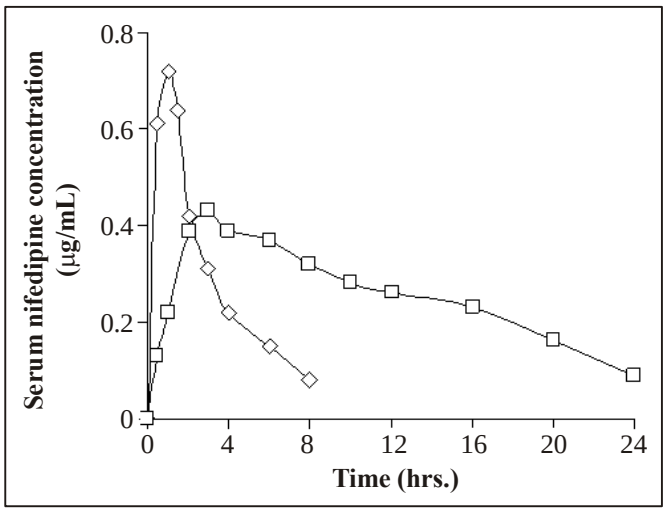

Fig. 1: Serum concentrations of nifedipine following oral administration of nifedipine soft capsules (◊) and its starch acetate CR microcapsules (□)

A very rapid absorption of nifedipine with a Ka of 2.05 h^{-1} was observed following the oral administration of nifedipine soft capsules. A C_{max} of 0.72 μg/mL observed at 1.0 h following the administration and later, the concentration decreased rapidly. The very rapid absorption of nifedipine soft capsules is due to the presence of nifedipine in solution form in the soft capsules.

Table 1: Summary of pharmacokinetic parameters estimation following the oral administration of nifedipine soft capsules and its starch acetate controlled release microcapsules

Pharmacokinetic parameter	Soft capsules	CR microcapsules
C_{max} (μg/mL)	0.72	0.43
T_{max} (h)	1.0	3.0
K_{el} (h^{-1})	0.253	-
$t_{1/2}$ (h)	2.739	-
$(AUC)_o^\infty$ (μg.h /mL)	4.47	6.30
BA (%)	100	140.94
K_a (hr^{-1})	2.049	0.177
MRT (h)	2.53	9.60

The elimination rate constant (K_{el}) and biological half – life ($t_{1/2}$) were found to be 0.253 h^{-1} and 2.74 h, respectively following the administration of nifedipine soft capsules. The $t_{1/2}$ value estimated is in good agreement with the earlier reported[5] value of 2 – 3 h. MRT was found to be 2.53 h following the administration of nifedipine soft capsules.

When starch acetate microcapsules were administered, slow absorption of nifedipine was observed. The absorption rate (K_a) was found to be 0.177 h^{-1} with starch acetate microcapsules, whereas it was 2.05 h^{-1} with soft capsules. A C_{max} of 0.43 μg/mL was observed at 3.0 h following administration of starch acetate microcapsules. C_{max} and T_{max} values also indicated slow absorption of nifedipine from starch acetate microcapsules.

The serum nifedipine concentrations were stabilized and maintained within a narrow range for longer periods of time in the case of microcapsules. The serum concentrations were decreased slowly. MRT was increased from 2.5 h for soft capsules to 9.60 h with starch acetate microcapsules indicating longer stay of drug in the body, when it was admistered in starch acetate microcapsules. The relative bioavailability of nifedipine from starch acetate microcapsules was 140.94%, when compared to soft capsules (100%).

Thus, the starch acetate microcapsules exhibited good release retarding and rate controlling effect *in vivo*. Nifedipine was released and absorbed slowly over longer periods of time *in vivo* resulting in the maintenance of serum concentrations within a narrow range over longer period time following the administration of starch acetate microcapsules of nifedipine.

CONCLUSIONS

(i) Nifedipine absorption was rapid with a rate constant (K_a) of 2.05 h^{-1} in case of soft capsules, whereas with starch acetate microcapsules, the absorption was slow over longer periods of time with a K_a of 0.177 h^{-1}.

(ii) MRT was increased from 2.5 h for soft capsules to 9.6 h with starch acetate microcapsules indicating longer stay of drug in the body, when administered as starch acetate microcapsules.

(iii) The relative bioavailability of nifedipine from starch acetate microcapsules was (140.94%), when compared to soft capsules (100%).

(iv) Starch acetate microcapsules exhibited good release retarding and rate controlling effect *in vivo*. Nifedipine was released and absorbed slowly over longer periods of time *in vivo* resulting in the maintenance of serum concentrations within a narrow range over longer periods of time.

REFERENCES

1. K. P. R. Chowdary and G. V. Radha, Int. J. Chem. (2009) (in Press).

2. Katsumi Miyazaki, Naonori Khori and Takaichi Arita, J. Chromatogr., **310**, 219, (1984).

3. J. G. Wagner and E. Nelson, J. Pharm. Sci., **52**, 610 (1963).

4. J. G. Wagner and E. Nelson, J. Pharm. Sci., **53**, 1392 (1964).

5. Syed Lalik Ali, Nifedipine, in, Analytical Profiles of Drug Substances, Kluas Florey (Ed.), **18**, Academic Press Inc., New York, San Francisco and London (1989) p. 273.

Accepted : 01.01.2011