Asian Journal of Chemistry Vol. 21, No. 6 (2009), 4199-4204

Pharmacokinetic Evaluation of Natural Resin Coated Microcapsules of Nifedipine

K.P.R. CHOWDARY*, PRITHWIRAJ MOHAPATRA and M.N. MURALI KRISHNA
University College of Pharmaceutical Sciences,
Andhra University, Visakhapatnam-530 003, India
E-mail: profkprc@rediffmail.com

Resin coated microcapsules of nifedipine were prepared by emulsification-solvent evaporation method employing (i) olibanum resin and (ii) colophony as coat materials and were subjected to pharmacokinetic evaluation with an objective to evaluate their release retarding and rate controlling efficiency *in vivo*. Nifedipine release from the resin coated microcapsules was slow and spread over 24 h. In the *in vivo* study, the rapid absorption of nifedipine with a rate constant (K_a) of 4.51 h^{-1} was observed following the oral administration of nifedipine soft capsules. The absorption of nifedipine was slow over longer periods of time with a rate constant (K_a) of 0.124 and 0.134 h^{-1} with olibanum and colophony coated microcapsules, respectively. The mean residence time (MRT) was found to be increased from 3.43 h for soft capsule to 10.9 h and 10.25 h, respectively with olibanum and colophony coated microcapsules indicating longer stay of the drug in the body when it was administered as resin coated microcapsules. The relative bioavailability of olibanum and colophony coated microcapsules was 126.75 and 113 %, respectively when compared to soft capsules (100 %).

Key Words: Nifedipine, Microcapsules, Olibanum, Colophony, Pharmacokinetics.

INTRODUCTION

Microencapsulation and microcapsules are widely accepted for controlled release. Polymers and release retarding materials used as a coat play a vital role in controlling the drug release from the microcapsules. Though a variety of polymeric materials are available to serve as release retarding coat materials, there is a continued need to develop new, safe and effective release retarding coat materials for microencapsulation. We reported earlier[1-4] two natural resins namely olibanum resin and colophony as new and efficient microencapsulating agents for controlled release and the microcapsules of nifedipine coated with these natural resins exhibited good controlled release characteristics *in vitro*. In the present study pharmacokinetic evaluation was done on the resin-coated microcapsules of nifedipine with an objective to evaluate the release retarding and rate controlling efficiency of olibanum resin and colophony *in vivo*.

EXPERIMENTAL

Nifedipine is a gift sample from M/s Cipla Ltd., Mumbai. Chloroform GR (Merck), diethyl ether (Qualigens), methanol (Qualigens), sodium carboxy methyl cellulose (sodium CMC having a viscosity of 1500-3000 cps of a 1 % w/v solution at 25 ºC) and sodium lauryl sulphate (Loba chemie) were used.

The olibanum resin used as coat material was extracted from olibanum in the laboratory as follows: Powdered olibanum (10 g) was extracted repeatedly with 4 × 50 mL quantities of solvent ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40 ºC. The dry mass was powdered and the size was reduced to 200 mesh.

Colophony resin obtained from commercial sources was purified as follows: Powdered colophony (10 g) was extracted repeatedly with 4 × 50 mL quantities of solvent ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40 ºC. The dry mass was powdered and the size was reduced to 120 mesh.

Methods

Preparation of microcapsules: An emulsification-solvent evaporation method was tried to prepare resin-coated microcapsules. Resin (0.2 g) was dissolved in chloroform (5 mL) to form a homogeneous solution. Core material, nifedipine (0.8 g) was added to the polymer (resin) solution (5 mL) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 mL of an aqueous mucilage of sodium CMC (0.5 % w/v) contained in a 450 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi medium duty stirrer with speed meter (Model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28 ºC) for 3 h to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules.

Estimation of nifedipine: Nifedipine content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 238 nm in phosphate buffer of pH 6.8. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 1-10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 %, respectively.

Drug release study: Release of nifedipine from the resin-coated microcapsules was studied in phosphate buffer of pH 6.8 containing 1 % SLS (900 mL) using an 8 station dissolution rate test apparatus (model Disso-2000, M/s Lab India) with a paddle stirrer at 50 rpm and 37 ± 0.5 ºC as prescribed for nifedipine extended release tablets in USP XXIV. A sample of microcapsules equivalent to 20 mg of nifedipine were used in each test. Samples (5 mL) were withdrawn through a filter

(0.45 µ) at different time intervals over 24 h and were assayed at 238 nm for nifedipine using a Shimadzu UV-150 double-beam spectrophotometer. The sample (5 mL) taken at each sampling time was replaced with fresh dissolution medium (5 mL). The drug release experiments were conducted in triplicate.

Pharmacokinetic study design and protocol: *In vivo* study design and protocol was approved by Institutional Ethical Committee. Four healthy rabbits of either sex, weighing 200-250 g were used (n = 4). A crossover experimental design with a wash out period of 1 month was followed for testing the products. The products were administered orally in the morning following overnight fasting. No food or liquid other than water was permitted until 4 h following the administration of the product.

After collecting the 'zero' hour blood sample (blank) the product in the study was administered orally with a glassful of water. 4 mL of blood samples were collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24 h after administration. The blood samples were centrifuged at 5000 rpm and the serum separated was collected into dry tubes and all the samples were stored under refrigerated conditions prior to assay. Serum concentrations of nifedipine were determined by a known HPLC method[5] as follows:

Methanol (100 µL) and acetonitrile (1 mL) were added to 0.5 mL of serum and agitated for 5 min with a cyclomixer. After centrifugation at 5000 rpm for 5 min, 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 then centrifuged at 5000 rpm for 5 min. 4.5 mL of the organic layer was transferred to a boiling tube and evaporated to dryness at 40 ºC 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) and 20 µL of the solution was injected into the HPLC (Shimadzu) column (C-18 RP 250 × 4.6 mm. D; Particle size: 5 µm).

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 ($t_{1/2}$), per cent absorbed to various times and absorption rate constant (K_a) were calculated in each case as per known standard methods[6,7].

RESULTS AND DISCUSSION

Resin coated microcapsules of nifedipine could be prepared by the Emulsification-solvent evaporation method with both olibanum resin and colophony. The microcapsules were found to be discrete, spherical and free flowing. Low coefficient of variation in per cent drug content (< 1 %) indicated uniformity of drug content in a batch of microcapsules. Microencapsulation efficiency was in the range of 96-99 %. Nifedipine release from the resin coated microcapsules was slow and spread over 24 h (Fig. 1). Drug release from the resin coated microcapsules was by fickian diffusion mechanism.

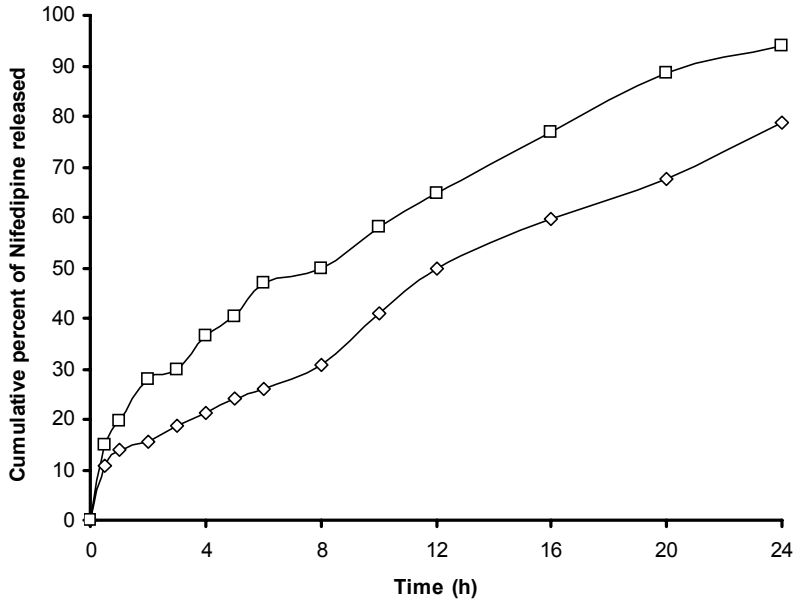

Fig. 1. Drug release profiles of O-MC microcapsules (-◇-); C-MC microcapsules (-□-)

Olibanum resin coated microcapsules (O-MC) of size 443 µm and containing 91.2 % nifedipine and colophony resin coated microcapsules (C-MC) of size 443 µm and containing 79.0 % nifedipine were subjected to pharmacokinetic evaluation as these microcapsules provided slow and controlled *in vitro* drug release over 24 h fulfilling the USP XXIV release prescribed for nifedipine extended release tablets. Nifedipine soft capsules were used as reference standard. Time *vs.* serum concentration profiles of various nifedipine products tested are shown in Fig. 2. A summary of the pharmacokinetic parameters estimated following the oral administration of various nifedipine products is given in Table-1.

The elimination rate constant (K_{el}) for nifedipine was found to be 0.2412 h^{-1} and the corresponding biological half-life ($t_{1/2}$) was found to be 2.87 h following the oral administration of nifedipine soft capsules. The $t_{1/2}$ value of nifedipine obtained in the present work is in good agreement with the earlier reported value[8] of 2-3 h. The mean residence time (MRT) was found to be 3.43 h. These values of $t_{1/2}$ and MRT indicated the rapid elimination of nifedipine in the body when administered as a solution in soft capsules.

Application of Wagner-Nelson method to the serum concentration data indicated a rapid absorption of nifedipine following the oral administration of nifedipine soft capsules. The absorption was 98.9 % in 1.0 h and the absorption rate constant (k_a) was 4.51 h^{-1}. A C_{max} of 70.70 ng/mL was observed at 1 h after the administration of nifedipine soft capsules and later the concentration was decreased rapidly. The rapid absorption of nifedipine from soft capsules is due to the presence of nifedipine in solution from in the soft capsules.

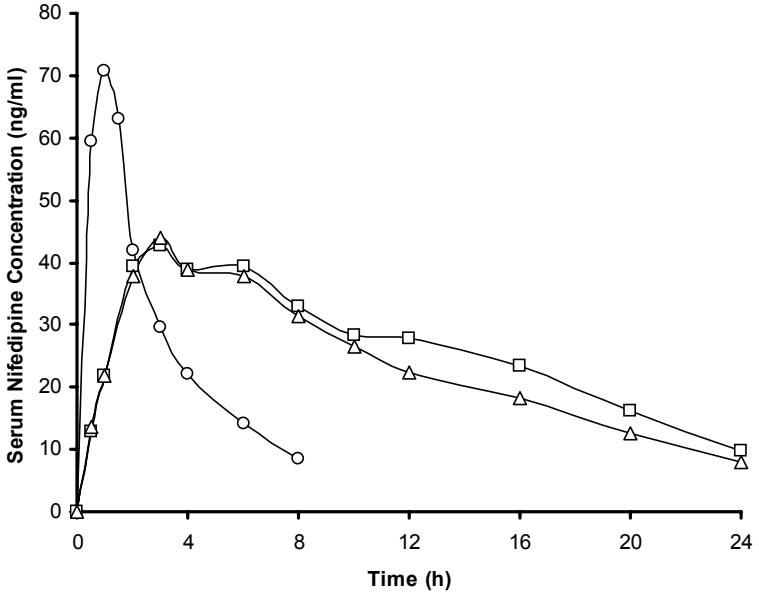

Fig. 2. Serum concentrations of nifedipine following the oral administration of various nifedipine products in rabbits; nifedipine soft capsules (-**o**-); O-MC microcapsules (-**□**-); C-MC microcapsules (-**Δ**-)

TABLE-1
SUMMARY OF PHARMACOKINETIC PARAMETERS ESTIMATED FOLLOWING THE ORAL ADMINISTRATION OF VARIOUS NIFEDIPINE PRODUCTS IN RABBITS

Product	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	$(AUC)_0^\infty$	BA (%)	K_a (h^{-1})	Per cent absorbed (h)				MRT (h)
							1	4	8	12	
A	70.70	1.0	2.87	262.8	100.0	4.510	98.9	-	-	-	3.43
B	42.70	3.0	6.36	666.4	126.7	0.124	15.4	42.9	61.8	76.1	10.90
C	44.05	3.0	6.58	594.1	113.0	0.134	17.3	48.2	67.5	79.2	10.25

A = Nifedipine soft capsules; B = O-MC microcapsules; C = C-MC microcapsules.

When the resin coated microcapsules were administered orally, the serum concentrations were found to be lower than those observed with nifedipine soft capsules indicating slow absorption of nifedipine from both the resin coated microcapsules. A C_{max} of 42.70 and 44.05 ng/mL was observed at 3 h after administration of O-MC and C-MC microcapsules, respectively. Application of Wagner-Nelson method to the serum concentration data also indicated slow absorption of nifedipine from the resin coated microcapsules. The absorption rate constant (K_a) was found to be 0.124 and 0.134 h^{-1}, respectively with O-MC and C-MC microcapsules. The serum nifedipine concentrations were stabilized and maintained within a narrow range for longer periods of the time in the case of resin coated microcapsules. For example the serum concentrations were maintained in the range 20-40 ng/mL during the

period from 1.0 to 16.0 h in the case of resin coated microcapsules; whereas in the case of soft capsules the serum concentration was maintained in this range during the period from 0.5 to 5.0 h only. The mean residence time (MRT) was found to be increased from 3.43 h for soft capsule to 10.9 h and 10.25 h, respectively with O-MC and C-MC microcapsules indicating longer stay of the drug in the body when it was administered as resin coated microcapsules. The relative bioavailability of O-MC and C-MC microcapsules was 126.75 and 113 %, respectively when compared to soft capsules (100 %).

The pharmacokinetic evaluation, thus, indicated that nifedipine from the resin coated microcapsules was released and absorbed slowly over longer period of time *in vivo* resulting in the maintenance of serum concentrations with in a narrow range over a longer period of time.

Conclusion

(i) Nifedipine release from the resin coated microcapsules was slow and spread over 24 h. (ii) Nifedipine absorption was rapid with a K_a of 4.51 h^{-1} in the case of soft capsules. Whereas with resin coated microcapsules the absorption of nifedipine was slow over longer periods of time with a K_a of 0.124 and 0.134 h^{-1} with olibanum and colophony coated microcapsules, respectively. (iii) The mean residence time (MRT) was increased from 3.43 h for soft capsule to 10.9 h and 10.25 h, respectively with olibanum and colophony coated microcapsules indicating longer stay of the drug in the body when it was administered as resin coated microcapsules. (iv) The relative bioavailability of olibanum and colophony coated microcapsules was 126.75 and 113 %, respectively when compared to soft capsules (100 %). (v) The pharmacokinetic evaluation, thus, indicated that nifedipine from the resin coated microcapsules was released and absorbed slowly over longer period of time *in vivo* resulting in the maintenance of serum concentrations with in a narrow range over a longer period of time.

REFERENCES

1. K.P.R. Chowdary and P. Mohapatra, *Int. J. Chem. Sci.*, **5**, 1397 (2007).
2. K.P.R. Chowdary, P. Mohapatra and M.N. Murali Krishna, *The Indian Pharmacist*, **6**, 61 (2007).
3. K.P.R. Chowdary, P. Mohapatra and M.N. Murali Krishna, *Indian J. Pharm. Sci.*, **68**, 461 (2006).
4. K.P.R. Chowdary and P. Mohapatra, *Int. J. Chem. Sci.*, **4**, 747 (2006).
5. K. Miyazaki, N. Khori and T. Arita, *J. Chromatogr.*, **310**, 219 (1984).
6. J.G. Wagner and E. Nelson, *J. Pharm. Sci.*, **52**, 610 (1963).
7. J.G. Wagner and E. Nelson, *J. Pharm. Sci.*, **53**, 1392 (1964).
8. S.L. Ali, in ed.: K. Florey, Nifedipine, Analytical Profiles of Drug Substrances, Academic Press INC., New York, San Francisco and London, Vol. 18, p. 273.

(*Received*: 29 January 2008; *Accepted*: 2 March 2009) AJC-7312