Release Studies of Nimesulide from Ethyl Cellulose and Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose Matrices

K.E.V. NAGOJI*, S. SRINIVASA RAO AND M.E. BHANOJI RAO
Roland Institute of Pharmaceutical Sciences, Berhampur - 760 010

Accepted 20 September 2000
Revised 5 September 2000
Received 28 March 1999

Spherical matrices of nimesulide were prepared by using ethyl cellulose alone and a combination of ethyl cellulose and hydroxy propyl methyl cellulose by spherical agglomeration technique and the drug release from these matrices 20/40 and 40/60 size was studied for 8 h. It was found that the drug release from ethyl cellulose matrices was slow compared to that from the combined polymer matrices. The improved drug release from the combined polymer matrices appears to be due to improved solubility of the drug in the presence of hydroxy propyl methyl cellulose.

Nimesulide is a non-steroidal antiinflammatory, analgesic and antipyretic agent. Chemically it is N-(4-nitro-2-phenoxyphenyl) methane sulfonamide. It is commonly prescribed for the treatment of cataract, asthma and in the treatment of inflammatory conditions associated with rheumatoid arthritis, respiratory tract infections, soft tissue and oral cavity inflammations, urogenital diseases and post operative pain[2]. It was reported that it has been well tolerated by most aspirin and/or NSAID intolerant patients[2]. Gastrointestinal disturbances like epigastric pain, heartburn, nausea, diarrhoea, vomiting, skin reactions (rash, pruritus) and CNS effects (dizziness, somnolence) are the most commonly reported adverse events of nimesulide[2]. However the incidence of these adverse events is less than those caused by other NSAIDs[2]

The objective of this study was to design a controlled release dosage form for nimesulide by forming spherical matrices by spherical agglomeration technique[3-4] which will help in releasing small quantities of drug and thereby reduce the intensity of adverse effects associated with the drug.

Nimesulide was obtained from Dr. Reddy's Laboratories, Hyderabad as a gift sample. Ethyl cellulose and hydroxy propyl methyl cellulose were purchased from Loba Chemie, Mumbai. Benzene used is of analytical grade purchased from E. Merck (India) Ltd, Mumbai.

*For Correspondence

Ethyl cellulose was dissolved in about 10 ml of benzene to form a homogenous polymer solution. Nimesulide was added to the polymer solution and mixed thoroughly with constant stirring for about 30 min. The mixture was heated on a water bath while stirring to evaporate benzene completely. The mass of matrices left behind was air dried for 24 h. The process was repeated with the combination of ethyl cellulose and hydroxy propyl methyl cellulose and the matrices so obtained were ground slightly in a mortar and the particles of 20/40 size and 40/60 size were separated. The drug content was estimated spectrophotometrically[5] using an ELICO SL 159 UV/Vis spectrophotometer. The results were presented in Table 1.

In vitro release of medicament from the spherical matrices of sizes 20/40 and 40/60 was studied using a six stage digital paddle dissolution test apparatus IP XXI in 900 ml of dissolution medium (one volume of phosphate buffer of pH 7.2 and three volumes of distilled water containing 8% *w/v* of tween 80), at a temperature of 37 ± 0.1° and at a speed of 100 rpm. A sample of matrices equivalent to 100 mg of nimesulide was taken in each test. Five millilitre aliquots of the dissolution medium was withdrawn for every one 1 h upto 8 h, Each sample was filtered and diluted with 0.1 N NaOH and analysed spectrophotometrically[5] at 436 nm for drug content. The cumulative percentage drug released was plotted against time as shown in Figs. 1 and 2. The $t_{1/2}$ and

TABLE : 1. PERCENTAGE OF NIMESULIDE PRESENT IN THE MATRICES AND DISSOLUTION CHARACTERISTICS

Coat polymer	Core:Coat ratio	Percentage of drug Present in the matrices		$t_{1/2}$ (h)		K x 10^2 h^{-1}	
		20/40	40/60	20/40	40/60	20/40	40/60
E.C.	3:1	76:50	76.75	21.39	10.20	3.24	6.79
E.C.	4:1	77.50	78.38	20.00	9.77	3.45	7.09
E.C.	9:1	85.00	87.50	6.70	3.39	10.34	20.43
E.C. + HPMC	3:1:1	55.00	58.75	4.05	1.89	17.11	36.69
E.C. + HPMC	4:1:1	63.75	67.50	5.38	2.57	12.88	26.95
E.C. + HPMC	9:1:1	78.75	82.00	6.18	2.83	11:12	24.41

EC = Ethyl Cellulose, HPMC = Hydroxy Propyl Methyl Cellulose. All values are average of three determinations.

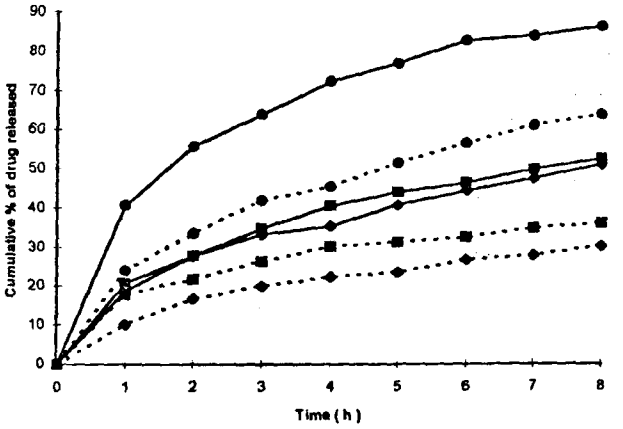

Fig. 1: *In vitro* release of nimesulide from ethyl cellulose matrices

***In vitro* release of nimesulide was monitored from EC matrices of the size 20/40 containing drug and EC in the ratio of 3:1 (-◆-), 4:1 (-■-) and 9:1 (-●-) and from 40/60 sized EC matrices containg drug and EC in the ratios of 3:1 (-◆-), 4:1 (-■-) and 9:1 (-●-)**

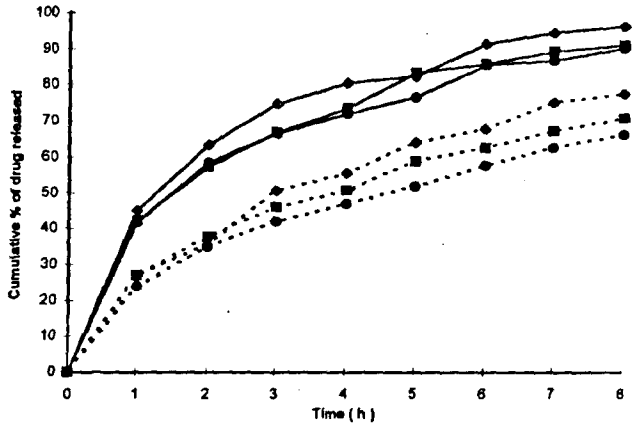

Fig. 2: *In vitro* release of nimesulife from EC and HPMC matrices

***In vitro* release of nimesulide was monitored from EC and HPMC matrices of the size 20/40 containing drug, EC and HPMC in the ratio of 3:1:1 (-◆-), 4:1:1 (-■-) and 9:1:1 (-●-) and from 40/60 sized EC and matrices containg drug and EC in the ratios of 3:1:1 (-◆-), 4:1:1 (-■-) and 9:1:1 (-●-)**

dissolution rate constants were calculated by using the 'equations for first order reactions'. The results were given in Table 1.

All the spherical matrices were found to be discrete and free flowing. They were sieved into different fractions of uniform sire (20/40 and 40/60 size) and the drug content in each fraction was found to be uniform. The results shown in Table 1 indicates uniformity in the composition of matrices. From the Table 1 it was also found that drug release from the spherical matrices, prepared with ethyl cellulose alone was very slow than from those prepared with the combination of ethyl cellulose and hydroxy propyl methyl cellulose. The drug release followed first order kinetics and depended on the size of the matrices and percentage of polymer. The drug release from ethyl cellulose matrices was found inversely proportional to the percentage polymer, whereas the drug release from the combined polymer matrices was found directly

proportional to the percentage polymer Eventhough the percentage of ethyl cellulose in combined polymer matrices was near to the percentage of ethyl cellulose in the single polymer matrices, the drug release was improved greatly. This directly proportional relationship between the drug release and percentage polymer in the case of combined polymer matrices may be due to the improved solubility of the nimesulide in the presence of hydroxy propyl methyl cellulose.

A good correlation was observed between the *percentage* of polymer and $t_{1/2}$ value (correlation coefficient values are 0.9636 ± 0.003, 0.9618 ± 0.007 in case of ethyl cellulose matrices of 20/40 size and 40/60 size respectively and 0.9347 ± 0.013, 0.9 ± 0.005 in case of combined polymer matrices of sizes 20/40 and 40/60, respectively) and between the percentage of polymer and drug release rate constant (correlation coefficient values are 0.9531 ± 0.009, 0.9510 ± 0.01 in case of ethyl cellulose matrices of sizes 20/40 and 40/60 and 0.9 ± 0.005, 0.9 ± 0.015 in case of combined polymer matrices of sizes 20/40 and 40/60, respectively).

ACKNOWLEDGEMENTS

The authors are grateful to Dr. Reddy's Laboratories, Hyderabad; M/s. Indoco Remedies Ltd., Mumbai; M/s. Bangalore Pharmaceutical & Research Laboratory Ltd., Bangalore; Stadmed Pvt. Ltd., Calcutta for providing gift samples of nimesulide and also to M/s. Roland Institute of Pharmaceutical Sciences, Berhampur for providing necessary facilities to carry out the research work.

REFERENCES

1. Budavari, S. Eds., In; The Merck Index, 12th Edn., Merck Research Laboratories, Division of Merck and Co. Inc., White House Station, N.J., 1996, 1125.
2. Davis, G. and Brogden, R.N., **Drugs**, 1994, 48, 431.
3. Kawashima, Y., Aoko, S., Takenaka, H. and Miyake, Y., **J. Pharm. Sci.**, 1984, 73, 1407.
4. Vimala Devi, M. and Sunita, A., **The Eastern Pharmacist**, 1992, 35, 177.
5. Nagoji, K.E.V., Srinivasa Rao S., Bhanoji Rao, M.E. and Kanna Rao K.V., **The Eastern Pharamacist**, 1999, 42, 117.
6. Martin, A., Bustamonte, P., In; Physical Pharmacy, 4 Edn, B.I. Waverly Pvt. Ltd., New Delhi.