Acta Pharm. 53 (2003) 263–273 Original research paper

Development and biopharmaceutical evaluation of osmotic pump tablets for controlled delivery of diclofenac sodium

MEENA RANI[1]*
RAHUL SURANA[2]
CHELLADURAI SANKAR[1]
BRAHMESHWAR MISHRA[1]**

[1] *Department of Pharmaceutics Institute of Technology Banaras Hindu University Varanasi-221005 (U.P.), India*

[2] *3M Pharmaceuticals 3M Center, St. Paul MN-55144, USA*

Received April 23, 2003
Accepted November 17, 2003

Based on the principles of an elementary osmotic pump (OP), OP tablets were designed and evaluated with the aim to deliver diclofenac sodium (DS) in a controlled manner. *In vitro* evaluation was done in various release media and kinetics was evaluated using the regression coefficient analysis. Effects of orifice size, coating membrane type, coating thickness, static and stirred conditions and pH variation were studied. *In vivo* evaluation was performed on six healthy human volunteers and various pharmacokinetic parameters (c_{max}, t_{max}, AUC_{0-24}, *MRT*) and relative bioavailability were calculated. The results were compared with the performance of two commercial tablets of DS. The drug release from OP tablets was dependent on the type and thickness of the coating membrane, but was independent of the orifice size and static and stirred conditions of the release medium. The OP tablets provided a prolonged and controlled DS release compared to commercial sustained-release and conventional tablets of DS.

Keywords: osmotic pump, diclofenac sodium, controlled release, bioavailability, pharmacokinetics

Studies of the controlled release of drugs for their extended and safe use have recently become an important field of research (1). Among controlled-release devices, osmotically driven systems hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero-order rates for prolonged periods (2–7). Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery (8–10). Preparation of an elementary osmotic pump consists of the core containing the active material and a semipermeable membrane that coats the core, having a microdrill produced orifice in order to release the active material. When the system happens to be inside the gastrointestinal tract, the fluid enters the core through the membrane and dis-

* Current address: Department of Pharmaceutics, University of Minnesota, MN-55455, USA

** Correspondence, e-mail: bmishra@banaras.ernet.in

solves the active material. The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate (11, 12). To gain the advantages of pH and agitation independent release performance leading to similar *in vitro/in vivo* delivery, osmotically active drug delivery systems have been extensively investigated (12–15).

Diclofenac sodium (DS) is a potent non-steroidal anti-inflammatory agent. It has a relatively short biological half-life and suffers from the hazards of adverse gastro-intestinal reactions. Therefore, the development of oral sustained/controlled release formulations of this drug is highly desirable. Many efforts have been made towards achieving sustained release formulations of DS (16–25). Hence, the present work was aimed to design, develop and evaluate an oral osmotic delivery system of DS, directed towards achieving a better therapeutic effect and bioavailability of this drug.

EXPERIMENTAL

Materials

Diclofenac sodium was obtained as a gift sample from Win-Medicare Ltd., India. Commercial tablets of DS [batches C10 (Voveran-SR) and C11 (Voveran- 2x50 mg conventional tablet)], each containing 100 mg drug, were the products of Novartis India, Ltd. (India). Cellulose acetate (CA), polyethylene glycol (PEG 400) and microcrystalline cellulose were obtained from Thomas Baker (Chemicals) Ltd., Glaxo Lab Ltd. and S.D. fine Chem. Ltd., all from India. All other chemicals/reagents used were of analytical grade, except for those used in HPLC analysis, which were of HPLC grade.

Preparation of osmotic pump tablets of DS

Preparation of core tablets. – Accurately weighed quantities of ingredients mentioned in Table I were passed through sieve No. 85 (aperture size 180 μm, British Standard). All the ingredients, except lubricant (magnesium stearate), glidant talc and binder polyvinylpyrrolidone (PVP), were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistered with aqueous solution of 10% (*m/V*) PVP, and granulated through sieve No. 18 (aperture size 1000 μm, US Standard) and dried in a hot air oven at 60 °C for sufficient time (3 to 4 hours) so that the moisture content of the granules reached 2–4%. The dried granules were passed through sieve No. 26 (aperture size 710 μm, US Standard) and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (300 mg each) using 10-mm diameter, deep concave punches. The compression force was adjusted to give tablets with approximately 7 kg cm^{-2} hardness on a Monsanto tablet hardness tester (Campbell Electronics, India).

Coating of core tablets. – Core tablets were film coated with either a semipermeable membrane of 2% (*m/V*) cellulose acetate (CA) in acetone with castor oil (20%, *m/m*, total solid CA) as plasticizer or with a microporous membrane consisting of PEG 400 (20%, *m/m*, total solid CA) incorporated in CA using a conventional laboratory model, stainless steel, 10-cm pear shaped, baffled coating pan. The manual coating procedure used

Table I. Composition and physical parameters of fabricated osmotic pump tablets

Ingredient (mg per OP tablet)	Batch code									
	OPIa	OPIb	OPIc	OPId	OPIIa	OPIIb	OPIIc	OPIId	OPIIIa	OPIVb
DS	100	100	100	100	100	100	100	100	100	100
MCC	182	182	182	182	142	142	142	142	122	117
Potassium chloride	–	–	–	–	40	40	40	40	60	40
Potassium bicarbonate	–	–	–	–	–	–	–	–	–	25
SLS	12	12	12	12	12	12	12	12	12	12
Talc	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Nature of coating	SP	SP	SP	MP	SP	SP	SP	MP	SP	SP
Coat thickness (μm)	40.1 ± 4.9	39.8 ± 4.4	40.2 ± 5.0	40.0 ± 4.8	40.0 ± 5.0	80.2 ± 4.5	100.2 ± 4.2	40.2 ± 4.8	40.1 ± 5.0	79.9 ± 4.9
Orifice diameter (μm)	–	500	1000	–	500	500	500	–	500	500

[1] OP – osmotic pump tablet; [2] DS – diclofenac sodium; [3] MCC – microcrystalline cellulose;
[4] SLS – sodium lauryl sulphate; [5] SP – semi-permeable; [6] MP – microporous

was based on an intermittent spraying and drying technique and an orifice through the membrane was made by a microdrill on one side of the tablet (26).

In vitro *studies*

In vitro studies were done using a USP 24 (27) dissolution apparatus II in different release media (pH 7.4, pH 6.8, distilled water) maintained at 37 ± 0.2 °C and 100 rpm. Withdrawn samples were analyzed on a Jasco UV/VIS spectrophotometer (model 7800, Jasco, Japan) at 275 nm. The experiments were performed in triplicate. To study the effect of agitation intensity, *in vitro* studies were performed at 50 rpm, 100 rpm and under static conditions. Under static conditions, samples were taken at different times after uniform mixing of the medium (10).

In vivo *studies*

In vivo studies were performed following the standard protocols in six healthy human volunteers of either sex weighing 55–75 kg and 24–29 years old in a cross-over design. Volunteers agreed in writing to participate in the study after being informed about the experimental protocol. All subjects were in good health according their medical history and complete physical examination. The volunteers neither smoked nor were on

any kind of medication before or during the experiment. The experiment protocol was approved by the Ethical Committee, BHU, India.

The modified HPLC method (28) was used to analyze human plasma samples, (stored at –20 °C until analysis) at different time intervals up to 24 hours following oral administration of formulated OP tablets as well as two commercial tablets (C10 and C11) to human subjects. Isocratic HPLC procedure was carried out using Novapak C-18, 4 μm (150×3.9 mm), column (Shimadzu, Japan) and acetonitrile 0.025 mol L^{-1} ammonium acetate (40:60) as a mobile phase at a flow rate of 1 mL min^{-1}. Injected volume was 75 μL and detection was performed at 275 nm using a UV detector (Shimadzu).

Statistical analysis

Experimental results were expressed as mean ± SD values. Student's *t* test was performed to determine the level of significance. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The core of OP tablets contained the drug, microcrystalline cellulose (MCC) as diluent, potassium chloride and potassium bicarbonate as osmogents, sodium lauryl sulphate (SLS), a surfactant for proper core wetting with imbibition medium, talc as glidant and magnesium stearate as lubricant. The various physical parameters evaluated for all fabricated OP tablets were found to be within official limits. It was observed from release profiles (Fig. 1) that an increase in membrane thickness affected the drug release rate inversely. All three tablets (OPIIa, OPIIb, OPIIc) exhibited constant and controlled drug release profiles from one hour onwards, though showing slow drug release till the first hour, which must have elapsed in inhibition of the core with the release medium. The drug release from the osmotic pump tablets batches OPId and OPIId (coated with a

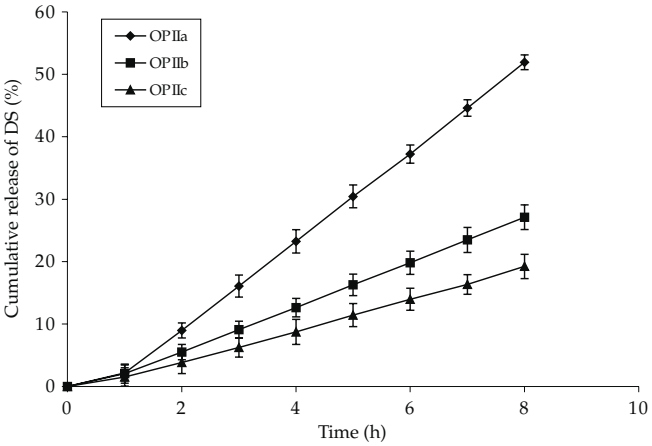

Fig. 1. *In vitro* release profiles showing the effect of coating thickness on DS release from OP tablets in pH 7.4 buffer. Bars represent SD values (n = 3).

membrane that becomes microporous due to dissolution of PEG 400 by the medium), followed the Higuchi kinetics and diffusion mechanism of drug release as compared to OPIb and OPIIa batches (coated with a semipermeable membrane) that exhibited zero--order kinetics of drug release (Table II). OPId and OPIId batches gave higher and non--linear drug release profiles (Fig. 2) due to the fact that when they came in contact with the aqueous environment during the release study, the water soluble PEG 400 leached out leaving behind the microporous membrane on the surface of the core tablet, which allowed free diffusion of drug molecules along the concentration gradient. Membranes in OPIb and OPIIa batches behaved like true semi-permeable membranes, resulting in zero-order delivery of drug through the orifice only under the control of osmotic pressure gradient across the membrane, as evidenced by the kinetic data shown in Table II.

Table II. Kinetics of in vitro *DS release from different batches of osmotic pump tablets*[a]

Batch code	Regression coefficient (R)		
	Zero-order	First-order	Higuchi
OPIa	0.9998	0.8900	0.9948
OPIb	0.9954	0.9134	0.9308
OPIc	0.9953	0.8935	0.9314
OPId	0.9864	0.9297	0.9980
OPIIa	0.9999	0.9154	0.9895
OPIIb	0.9999	0.9410	0.9894
OPIIc	0.9997	0.9473	0.9876
OPIId	0.9860	0.9270	0.9978
OPIIIa	0.9999	0.8855	0.9911
OPIVb	0.9999	0.9375	0.9902

[a] Analyzed by the regression coefficient method.

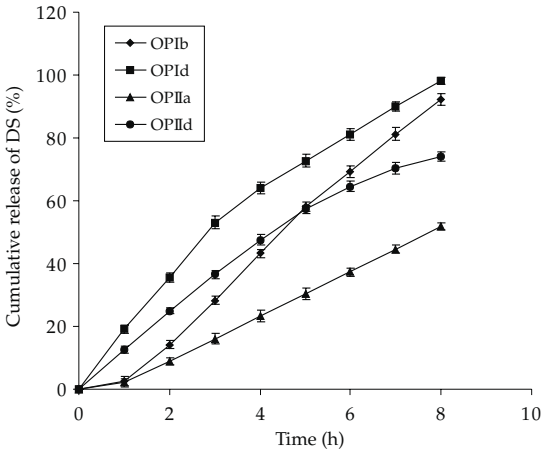

Fig. 2. *In vitro* release profiles showing the effect of semipermeable (batches OPIb and OPIIa) and microporous coating (batches OPId and OPIId) on DS release from OP tablets in pH 7.4 buffer. Bars represent SD values (n = 3).

Though the DS release decreased with an increase in coating thickness (Fig. 1), variation in orifice size (500 and 1000 μm) showed no significant effect on the rate and extent of DS release from OP tablets (Fig. 3). Since no burst effect was observed during the drug release study, it can be inferred that the two selected orifice sizes (500 and 1000 μm) had successfully prevented the membrane from rupturing by effectively releasing the hydrostatic pressure developed inside the system and at the same time delivered the drug at a constant rate over a sufficiently long period of time (12, 29). In order to simulate complete blocking of the delivery orifice, the release of DS from coated OP tablets without an orifice (OPIa) was studied (Fig. 3). Profiles exhibited prolonged drug release but with linearity maintained after 2 hours of lag period. This is in agreement with our earlier studies on osmotic pump tablets of naproxen sodium (10), wherein we reported that continuous water influx into the system produced an increase in the volume of the

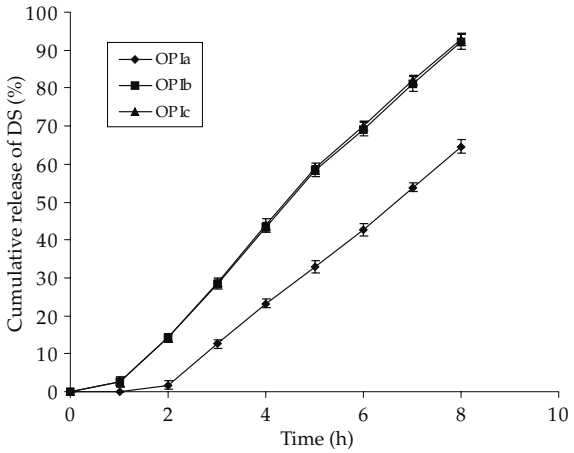

Fig. 3. *In vitro* release profiles showing the effect of orifice size (no orifice OPIa), 500 μm (OPIb) and 1000 μm (OPIc) on DS release from OP tablets in pH 7.4 buffer. Bars represent SD values (n = 3).

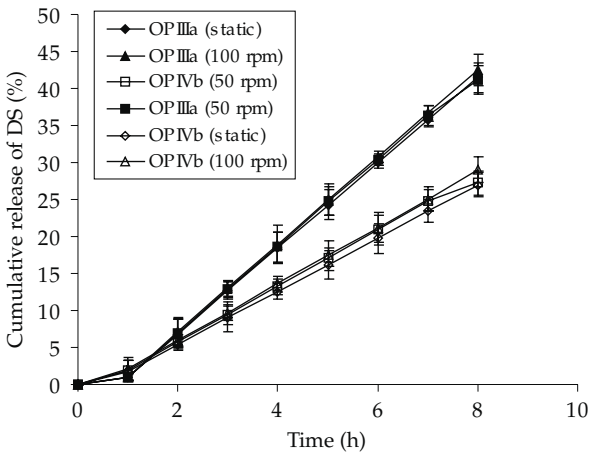

Fig. 4. *In vitro* release profiles showing the effect of agitational intensity variation on DS release from OP tablets in pH 7.4 buffer. Bars represent SD values (n = 3).

drug solution inside the coated tablet (without orifice) and this led to an increase of the hydrostatic and osmotic pressure inside the tablet. The pressure thus generated caused expansion and/or weakening of the membrane, which in turn led to the formation of pore(s) in the membrane or increased the size of the existing micropores, thereby delivering the contents *via* an osmotic delivery mechanism. This clearly indicates that even in the case of accidental blockage of the orifice of OP tablets, it is likely that there will be neither dose dumping nor failure of drug delivery and drug release may still follow a zero-order release pattern.

It was observed (Fig. 4) that the osmotic pump tablets OPIIIa and OPIVb having the same orifice diameter (500 μm) but different coat thickeness (40 and 80 μm, respectively) studied under stirred and static conditions exhibited no significant difference in the rate and extent of DS release. However, OPIVb tablets having coating membranes twice as

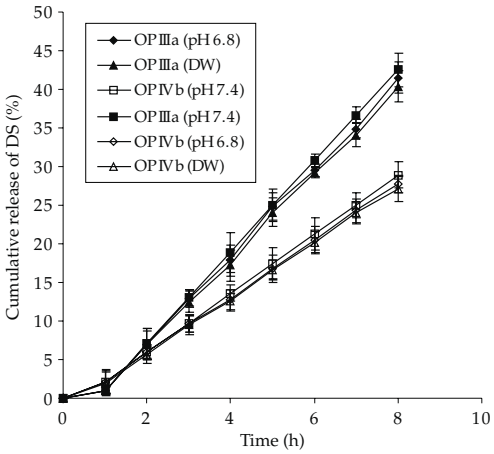

Fig. 5. *In vitro* release profiles showing the effect of pH variation on DS release from OP tablets. Bars represent SD values (n = 3).

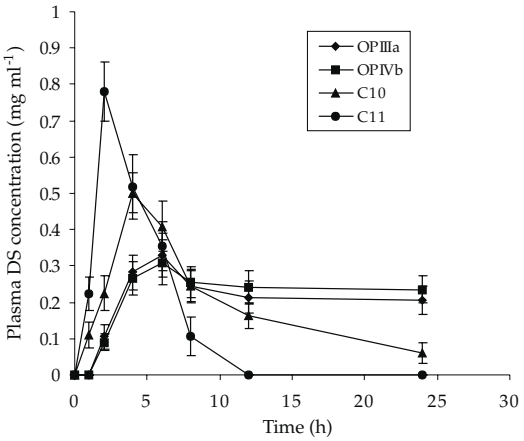

Fig. 6. Plasma profiles of DS following oral administration of fabricated osmotic pump (OPIIIa and OPIVb) tablets in comparison to commercial SR (C10) and conventional (C11) tablets to healthy human subjects. Bars represent SD values (n = 6).

thick as OPIIIa exhibited a significantly reduced rate and extent of drug release compared to the latter. Drug release from OP tablets performed in phosphate buffers of pH 7.4 and pH 6.8, and in water also resulted in a non-significant difference in DS release from OP tablets (Fig. 5) (30, 31). The *in vitro* drug release kinetics of OP tablets was studied by the regression coefficient analysis (32), as shown in Table II. All OP tablets, except for OPId and OPIId tablets, showed zero-order kinetics of drug release. OPId and OPIId tablets with microporous coatings followed the Higuchi diffusion kinetics.

The plasma DS concentration *vs.* time profiles (Fig. 6) obtained from *in vivo* studies clearly show that OP tablets maintained a constant therapeutic DS concentration (33) within plasma even up to 24 hours, as compared to commercial formulations C10 and C11 which showed a higher rate of drug concentration decrease as a function of time. The fabricated OP tablets studied *in vivo* showed lower c_{max} (but within therapeutic range) (33) and higher t_{max} values than commercial tablets (C10 and C11) (Fig. 6). Lower c_{max} for OP tablets indicates the avoidance of intense pearcing, thus avoiding the risk of exceeding the maximum safe concentration. Higher t_{max} for OP tablets is indicative of drug release occurring at a slower rate than from commercial tablets. Significantly high-

Table III. Bioavailability and pharmacokinetic parameters

Batch code	c_{max} (μg mL^{-1})[a]	t_{max} (h)[a]	$AUC_{0\text{-}24}$ (μg mL^{-1})[a]	RB_1 (%)[a]	RB_2 (%)	*MRT* (h)
OPIIIa	0.331 ± 0.060	6.0 ± 0.2	4.98 ± 0.12	108	138	13.3
OPIVb	0.310 ± 0.061	6.0 ± 0.3	5.35 ± 0.22	116	148	14.8
C10	0.501 ± 0.054	4.0 ± 0.5	4.61 ± 0.28	100	128	8.6
C11	0.781 ± 0.081	2.0 ± 0.5	3.60 ± 0.28	78	100	3.7

[a] Mean ± SD (*n = 6)*
AUC – area under the curve
RB – relative bioavailability
RB_1 – with reference to C10 (SR Voveran – SR)
RB_2 – with reference to C11 (conventional Voveran)

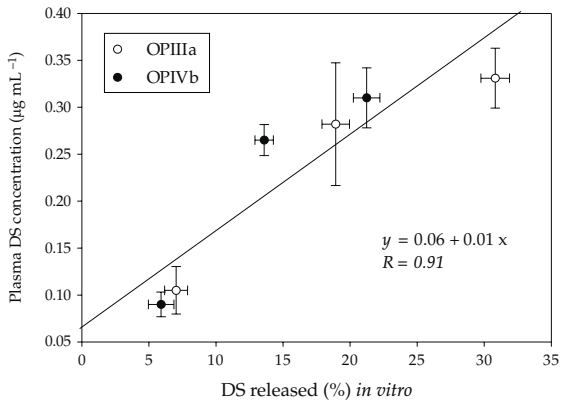

Fig. 7. Correlation between the *in vitro* percent DS release and plasma DS concentrations for fabricated osmotic pump tablets (OPIIIa and OP IVb) at 2, 4 and 6 hours.

er values of AUC_{0-24}, relative bioavailability and mean residence time (*MRT*) for OP tablets in comparison to C10 and C11 (Table III) further indicate the superiority of fabricated OP tablets over commercial SR (C10) and conventional (C11) tablets of DS, in terms of providing controlled drug release for longer time and improved bioavailability. Further, *in vitro* data and plasma DS concentration after 2, 4 and 6 hours for OPIIIa and OPIVb (Fig. 7) exhibited a good correlation (34, 35).

CONCLUSIONS

This study suggests that the OP tablets of DS could perform therapeutically much better than the commercial conventional DS tablets, as potential prolonged and controlled release dosage forms, which may lead to improved efficacy and better patient compliance.

Acknowledgement. – We thank Mr. Vinod Arora and Mr. Tausif (Ranbaxy Laboratories Ltd., Gurgaon, India) for providing HPLC facilities for carrying out *in vivo* studies.

REFERENCES

1. T. Salsa, F. Veiga and M. E. Pina, Oral controlled release dosage forms I. Cellulose ether polymer in hydrophilic matrices, *Drug Dev. Ind. Pharm.* **23** (1997) 929–938.
2. F. Theeuwes, Drug delivery systems, *Pharm. Ther.* **13** (1981) 149–191.
3. B. Eckenhoff, F. Theeuwes and J. Urquhart, Osmotically activated dosage forms for rate controlled drug delivery, *Pharm. Technol.* **5** (1981) 35–44.
4. B. Eckenhoff and S. I. Yum, The osmotic pump; novel research tool for optimizing drug regimens, *Biomaterials* **2** (1981) 89–97.
5. C. Bindschaedler, R. Gurny and E. Doelker, Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate, *J. Contr. Rel.* **4** (1986) 203–212.
6. R. K. Verma, B. Mishra and S. Garg, Osmotically controlled oral drug delivery, *Drug Dev. Ind. Pharm.* **26** (2000) 695–708.
7. R. K. Verma, D. M. Krishna and S. Garg, Formulation aspects in the developments of osmotically controlled oral drug delivery system, *J. Contr. Rel.* **79** (2002) 7–27.
8. G. Santus and R. W. Baker, Osmotic drug delivery; a review of patent literature, *J. Contr. Rel.* **35** (1995) 1–21.
9. R. K. Verma and B. Mishra, Studies on formulation and evaluation of oral osmotic pumps of nimesulide, *Pharmazie* **54** (1999) 74–75.
10. N. Ramakrishna and B. Mishra, Design and evaluation of osmotic pump tablets of naproxen sodium, *Pharmazie* **56** (2001) 958–962.
11. N. Ozdemir and J. Sahin, Design of a controlled release osmotic pump system of ibuprofen, *Int. J. Pharm.* **158** (1997) 91–97.
12. F. Theeuwes, Elementary osmotic pump, *J. Pharm. Sci.* **64** (1975) 1987–1991.
13. G. A. Mc Clelland, S. C. Sutton, K. Engle and G. M. Zentner, The solubility- modulated osmotic pump: *in vitro/in vivo* release of diltiazem hydrochloride, *Pharm. Res.* **8** (1991) 88–92.
14. S. Rose and J. F. Nelson, A continuous long-term injector, *Austral. J. Exp. Biol.* **33** (1995) 415–420.
15. G. Zentner, G. Rork and K. Himmelstein, The controlled porosity osmotic pump, *J. Contr. Rel.* **1** (1985) 269–282.

16. M. Rani and B. Mishra, Comparative evaluation of *in vitro* performance of commercial and fabricated sustained release diclofenac sodium tablets, *Ind. J. Pharm. Sci.* **63** (2001) 247–250.
17. M. Rani and B. Mishra, Effect of admixed polymers on diclofenac sodium release from matrix tablets, *Pharm. Pharmacol. Lett.* **11** (2001) 76–78.
18. M. Rani and B. Mishra, Development and evaluation of carbomer based matrices for the controlled delivery of diclofenac sodium, *Acta Pharm. Turc.* **41** (2003) 5–10.
19. G. Garcia-Encina, D. Torres, B. Seijo and J. L. Vila Jato, Formulation and *in vitro* evaluation of HPMCP-microencapsulated drug-resin complexes for sustained release of diclofenac, *Int. J. Pharm.* **121** (1995) 239–243.
20. E. A. Hosny, A. R. M. Al-Helw and M. A. Al-Dardiri, Comparative study of *in vitro* release and bioavailability of sustained release diclofenac sodium from certain hydrophilic polymers and commercial tablets in beagle dogs, *Pharm. Acta Helv.* **72** (1997) 159–164.
21. T. Nishihata, Simple formulation of sustained release tablets of diclofenac and examination in humans, *Int. J. Pharm.* **40** (1987) 125–128.
22. M. T. Sheu, H. L. Chou, C. C. Kao, C. H. Liu and T. D. Sokoloski, Dissolution of diclofenac sodium from matrix tablets, *Int. J. Pharm.* **85** (1992) 57–63.
23. B. Mishra, J. Panyam and A. V. Sharma, *In vitro* release of diclofenac sodium from multiple emulsions; effect of location of drug and pH of the aqueous phase, *Acta Pharm. Turc.* **41** (1999) 42–45.
24. C. H. Liu, Y. H. Kao, S. C. Chen, T. D. Sokoloski and M. T. Sheu, *In vitro* and *in vivo* studies of the diclofenac sodium controlled-release matrix tablets, *J. Pharm. Pharmacol.* **47** (1995) 360–364.
25. C. Sajeev, G. Vinay, R. Archna and R. N. Saha, Oral controlled release formulation of diclofenac sodium by microencapsulation with ethyl cellulose, *J. Microencap.* **19** (2002) 753–760.
26. N. Ramakrishna and B. Mishra, Plasticizer effect and comparative evaluation of cellulose acetate and ethylcellulose-HPMC combination coatings as semipermeable membranes for oral osmotic pumps of naproxen sodium, *Drug Dev. Ind. Pharm.* **28** (2002) 403–412.
27. United States Pharmacopoeia 24, National Formulary 19 United States Pharmacopoeial Convention, Inc., Rockville 2001, pp. 2051.
28. G. Giagoudakis and S. L. Markantonis, An alternative high-performance liquid-chromatographic method for the determination of diclofenac and flurbiprofen in plasma, *J. Pharm. Biomed. Anal.* **17** (1998) 897–901.
29. M. A. Ramadan and R. Tawashi, Effect of hydrodynamic conditions and delivery orifice size on the rate of drug release from elementry osmotic pump system (EOP), *Drug Dev. Ind. Pharm.***13** (1987) 235–248.
30. J. P. Skelly, L. A. Yamamoto, V. P. Shah, M. K. Yau and W. H. Barr, Topographical dissolution characterization for controlled release products: new technique, *Drug Dev. Ind. Pharm.* **12** (1986) 1159–1175.
31. J. P. Skelly, M. K. Yau, J. S. Elkins, L. A. Yamamoto, V. P. Shah and W. H. Barr, *In vitro* topographical characterization as a predictor of *in vivo* controlled release quindine gluconate bioavailability, *Drug Dev. Ind. Pharm.* **12** (1986) 1177–1201.
32. C. Sankar, M. Rani, A. K. Srivastava and B. Mishra, Chitosan based pentazocine microspheres for intranasal systemic delivery; development and biopharmaceutical evaluation, *Pharmazie* **56** (2001) 223–226.
33. W. Reiss, H. Sterlin, P. Degen, J. W. Faigle, A. Faigle, A. Geradin, J. Mopper, A. Sallman, A. Schmin, A. Schweizer, M. Sule, W. Thesbald and J. Wagner, Pharmacokinetics and metabolism of the anti-inflammatory agent voltaren, *Scand. J. Rheumatol.* **22** (1978) 17–29.
34. G. Levy, J. Leonards and J. A. Procknal, Development of *in vitro* tests which correlate quantitatively with dissolution rate limited drug absorption in man, *J. Pharm. Sci.* **54** (1965) 1719–1722.
35. V. P. Shah, V. K. Prasad, T. Alston, B. Cabina, R. P. Gural and M. C. Meyer, Phenytoin I: *in vitro* correlation for 100 mg phenytoin sodium capsules, *J. Pharm. Sci.* **72** (1983) 306–308.

S A Ž E T A K

Razvoj i biofarmaceutsko vrednovanje tableta diklofenak-natrija na principu osmotske pumpe

MEENA RANI, RAHUL SURANA, CHELLADURAI SANKAR i BRAHMESHWAR MISHRA

Na principu osmotske pumpe (OP) pripravljene su i evaluirane OP tablete diklofenak-natrija. *In vitro* evaluacija provedena je u različitim medijima. Proučavan je utjecaj veličine pora, vrste i debljine ovojnice, te utjecaj miješanja i pH na kinetiku oslobađanja. *In vitro* evaluacija provedena je na šest zdravih dobrovoljaca. Određeni su različiti farmakokinetički parametri (c_{max}, t_{max}, AUC_{0-24}, *MRT*) i relativna bioraspoloživost. Rezultati su uspoređivani s dvije vrste registriranih tableta diklofenak-natrija. Oslobađanje ljekovite tvari iz OP tableta ovisilo je o vrsti i debljini ovojnice, a nije ovisilo o veličini pora i uvjetima miješanja u mediju za oslobađanje. U odnosu na komercijalne tablete sa i bez produljenog oslobađanja DS-a, OP tabletama postignuto je produljeno i kontrolirano oslobađanje ljekovite tvari.

Ključne riječi: osmotska pumpa, diklofenak-natrij, kontrolirano oslobađanje, bioraspoloživost, farmakokinetika

Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P), India

3M Pharmaceuticals, 3M Center, St.Paul, MN-55144, USA