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Studies on Elementary Osmotic Pump Tablets of Naproxen Sodium

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Abstract

The present investigation embodies the development of elementary osmotic pump tablets(OPT) of Naproxen sodium (NS) for per-oral administration mainly with an objective to deliver a constant, pre-determined amount of drug in solution form for extended duration . Core tablets of OPT were prepared by compression using drug, different osmogens, microcrystalline cellulose (MCC), PVP and optional excipients like sodium lauryl sulphate(SLS) and sodium bicarbonate (SBC) on tabletting machine. Core tablets were coated using 2% w/v cellulose acetate dissolved in IPA:acetone (1:9) mixture. All the OPT were evaluated for physical parameters and in vitro drug release characteristics in sequenced gastrointestinal(GI) fluid. The observation of drug release from OPT indicated controlled and prolonged release of NS in comparison to standard marketed formulation of NS. The rate and extent of drug release from OPT were found to be dependent on the presence of different osmogens, SLS and SBC in the core and independent on agitation intensity of the release medium.

Key words. Naproxen sodium, Elementary Osmotic Pump, Osmotic pump tablet, Cellulose acetate

Introduction

Osmotic pressure was first employed as energy source to deliver active ingredients in the 1970s (Rose and Nelson 1955). Because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices in the past two decades. Various types of osmotic pumps were reviewed by Santus and Baker (1995).

The elementary osmotic pump (EOP) was introduced by Theeuwes(1975). The EOP consists of drug core containing osmogen, surrounded by a semipermeable membrane and drilled with a delivery orifice on one side. In operation, the drug/osmotic core acts by imbibing water from the surrounding medium via semi-permeable membrane, dissolving the drug and the osmogen and delivering the drug with constant rate under the effect of constant osmotic pressure generated inside the core. The EOP is very simple to prepare that delivers drug at an approximate zero-order rate (Theeuwes, 1975, Theeuwes and Higuchi 1972).

Naproxen sodium (NS) one of the popularly used non-steroidal anti-inflammatory drug , is used for long term treatment of rheumatoid arthritis and alkylosing spodilitis (Brodgen *et al,* 1979). Usual dose of NS as conventional tablet is 275 mg twice a day, patient compliance is often enhanced if the dosage schedule is decreased to once a day (Mroszceak *et al.* 1988). It was thought that a controlled and prolonged release product of NS might therapeutically be more beneficial than its conventional formulations. Hence, the present study was undertaken with an objective to develop EOP of NS that can deliver the drug as solution with controlled rate for larger duration. The EOP of NS is expected to significantly reduce the GI side effects by exposing the gastrointestinal mucosae to comparatively lesser amount of drug in solution form at a time as compared to other conventional formulations. The systemic adverse effects of NS may also be minimised due to continuous maintenance of drug concentrations within the

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therapeutic range, and therefore EOP is expected to perform therapeutically much better than the conventional products of NS.

Materials and Methods

Material : Naproxen sodium was received as a gift sample (Recon Ltd. Bangalore, India), cellulose acetate (39.8% acetylation) and polyvinylpyrrolidone (PVP K-15) (each from CDH, Delhi, India), propylene glycol (Reidal Indian Chemicals, Hapur, India), acetone, fructose, dextrose and mannitol (each from Qualigens Fine Chemicals, Mumbai, India), xylitol and inositol (each from S.D. Fine Chemicals Mumbai, India) were purchased. All other chemicals used were of analytical grade and used as received. USP XXI dissolution apparatus II (Decibal Instruments Chandigarh, India), UV/VIS spectrophotometer (JASCO Model 7800, Tokyo, Japan) were used during the study.

Equilibrium Solubility Study :The solubility of NS was determined in distilled water in the presence of different concentrations of osmotic agents (fructose, inositol, xylitol, dextrose, mannitol) by adding excess drug to solutions of various concentration of osmogens in closed container at 37 ± 0.2°C. Excess amount of drug was added to ensure saturation and the solutions were equilibrated for 24 . The saturated solutions were filtered and analysed on UV spectrophotometer at 317 nm after suitable dilution.

Tabletting : The formula described in Table (1) was used for preparation of core tablets of all the batches of OPT. Accurately weighed quantity of each ingredient was passed through sieve # 85. All the ingredients, except lubricant (Magnesium stearate), and glidant (talc) were manually blended homogeneously in mortar through geometric dilution. The mixture was wetted with the PVP 15% w/v aqueous solution and granulated through sieve # 18 and dried in hot air oven at 60°C for sufficient time (3-4) so that moisture content of granules reached 2-4%. The dried granules were passed through sieve # 22 and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets, each weighing 700 mg, on a single punch machine (Manesty E2, England) using concave punches of 12 mm diameter. The compression force was adjusted to give the tablets with hardness greater than 7 kg/m2 on a monsanto tablet hardness tester.

Table 1. Formula of the core formulation

S.No.	Ingredients (mg/tablet)	Batch No. of core formulation						
		I	II	III	IV	V	VI	VII
1.	Naproxen Sodium	400	400	400	400	400	400	400
2.	Fructose	40	-	-	-	-	40	40
3.	Inositol	-	40	-	-	-	-	-
4.	Xylitol	-	-	40	-	-	-	-
5.	Dextrose	-	-	-	40	-	-	-
6.	Mannitol	-	-	-	-	40	-	-
7.	Sodium bicarbonate	-	-	-	-	-	-	110
8.	MCC*	200	200	200	200	200	190	90
9.	SLS*	-	-	-	-	-	10	-
10	PVP*	50	50	50	50	50	50	50
11.	Talc	4	4	4	4	4	4	4
12.	Magnesium stearate	4	4	4	4	4	4	4

MCC = Microcrystalline cellulose, SLS = Sodium lauryl sulphate, PVP = Polyvinylpyrrolidone
– not used

Coating and Drilling : Cellulose acetate 2% w/v and castor oil 20% w/w of total solid CA (plasticizer) dissolved in the mixture of isopropyl alcohol and acetone in the ratio of 1:9 was used as a coating solution. The coating operation was performed for batch of around 100 tablets at a time in a conventional laboratory model stainless steel, 10 cm pear shaped, baffled coating pan (Scientific Instruments, New Delhi, India). The pan speed was 20 rpm and the coating solution was manually sprayed over the surface of the tumbling tablets with a spray gun. The inlet air temperature was 40-45°C and the manual coating procedure used was based on intermittent spraying and coating technique (Ramakrishna and Mishra, 2002). The coating weight and the thickness was controlled by the volume of coating solution consumed in the coating process. Coated tablets were allowed to dry completely in a hot air oven at 60°C and finished by standard polishing procedure. Specification of OPT of all batches have been shown in Table 2. An appropriate orifice size (0.5 mm) was drilled on one face of the all the OPT through membrane using microdrill (Ozdemir and Sahin 1997).

Table 2. Data for the physical parameters of OPT of NS [Mean ± S.D. (n = 10)]

S. No	Ingredients (mg/tablet)	Batch No. of core formulation						
		I	II	III	IV	V	VI	VII
1.	OPT weight (g)	0.7162 (0.0292)	0.6812 (0.2122)	0.7256 (0.0241)	0.7120 (0.0251)	0.7244 (0.0212)	0.7161 (0.0262)	0.7259 (0.0251)
2.	Thickness (mm)	5.4122 (0.1052)	5.1224 (0.2214)	5.4214 (0.1458)	5.2146 (0.1342)	5.1024 (0.1152)	5.6132 (0.1382)	5.1258 (0.1124)
3.	Diameter (mm)	12.7954 (0.0485)	12.7389 (0.2552)	12.7628 (0.0215)	12.7112 (0.0314)	12.5948 (0.05214)	12.6908 (0.0182)	12.5042 (0.0822)
4.	Drug content (%) (n = 20)	94.30 (1.98)	96.88 (2.24)	98.27 (2.46)	98.42 (2.52)	97.76 (2.28)	98.28 (1.52)	96.46 (3.97)
5.	Surface area*(cm^2)	3.8285	3.8142	3.8648	3.9924	3.6638	3.8652	3.9242
6.	Volume* (cm^3)	0.5246	0.5242	0.5498	0.4961	0.5216	0.5494	0.5282
7.	Coat thickness (μm)	39.8±4.5	38.9±4.2	41.53±3.9	39.9±3.8	40.87±4.1	39.9±4.3	41.2±3.8
8.	Orifice diameter (mm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5

* Calculated from geometry of device.

Evaluation of Formulations : All the OPT were inspected visually for the coating film smoothness, uniformity of coating, edge coverage, luster and tablet to tablet uniformity of the coating.Thickness and diameter of tablets were recorded before and after coating using standard screw gauze (Verma and Mishra, 1999).

Determination of coat thickness.: Coating of the formulation was peeled off, washed with distilled water and dried. Coat thickness was measured with the help of a screw gauze (Verma and Mishra 1999).

Orifice diameter: Average orifice diameter of an individual OPT was determined microscopically using precalibrated ocular micrometer (Verma and Mishra 1999).

Drug content: Naproxen sodium content in OPT was determined from a mixed powder sample of 20 tablets in each batch after dissolving in distilled water and assaying spectrophotometrically at 317 nm.

In vitro release study: In vitro release characteristics, in triplicate, of NS from various OPT were investigated using standard USP XXI dissolution apparatus II at either 50 rpm or 100 rpm for 8 . At time zero, an OPT was dropped in 900 ml of sequenced simulated GI fluid (simulated

gastric fluid of pH 1.2 for first followed by simulated intestinal fluid of pH 6.8 till 8 of study) equilibrated to 37 ± 0.2°C. 5 ml samples were withdrawn at different time intervals and analyzed spectrophotometrically at 329 nm.

Results and Discussion

The result of equilibrium solubility study indicated that different concentrations of osmogens (fructose, inositol, xylitol, dextrose and mannitol) could not bring any significant change in the solubility of NS in distilled water. This indicates that the solubilization of NS in the imbibed medium inside the core will remain unaffected by the presence of different osmogens in the core formulation, and therefore , the guiding factor for drug delivery from the core is expected to be the osmotic pressure gradient only. The data for various physical parameters of OPT shown in Table 2 exhibited the values being within the limits. Release profiles of NS showing effects of different osmotic agents are shown in Fig.1. Presence of different concentrations of osmotic agents (fructose, inositol, xylitol, dextrose and mannitol) were not shown any significant change in the solubility of NS. All the OPT exhibited almost similar rate and lower extent of drug release till one hour followed by faster and constant rate of drug release till 5 with subsequent slow down in drug release from 5 onwards till 8 of the study. The low rate and extent of drug release till one hour is attributed to imbibition period of drug core with the release medium. The constant and continuous drug release beyond one hour is attributed to be under the effect of constant osmotic pressure generated in the core due to saturated solution of drug and the osmotic agent caused by their dissolution in the imbibed release medium in the core. According to Theeuwes 1975, the osmotic pressure has direct influence on the rate and extent of drug release. On the same pattern, fructose (batch I) in our studies, has given maximum rate and extent of NS release, as fructose generates much higher osmotic pressure (Zentner *et al.*, 1990) than other osmotic agents inositol (batch II), xylitol (batch III), dextrose (batch IV) and the mannitol (batch V) which gave the lowest rate and

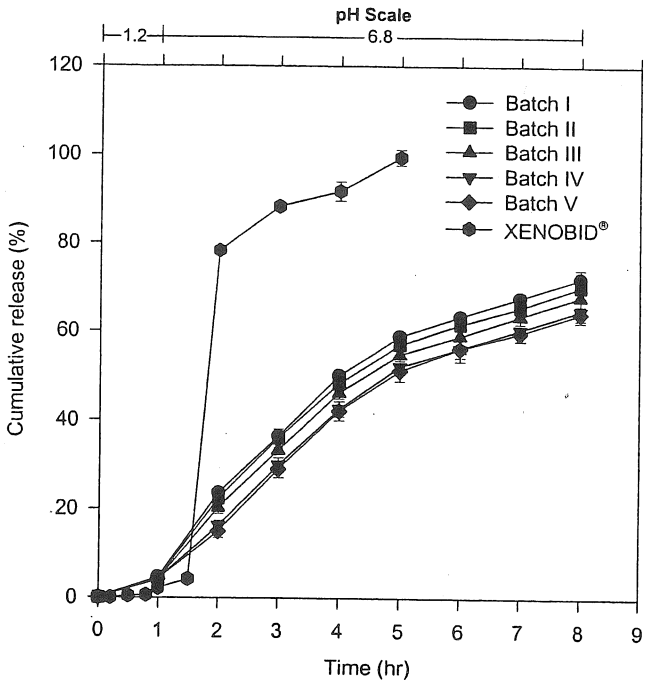

Fig.1 Profiles showing effect of different osmotic agents on NS release from OPT in sequenced GI fluid at 50 rpm. Bars represent ±S.D. (n=3).

extent of drug release due to comparatively lower osmotic pressure generated by mannitol in the core. The difference in the rate and extent of drug release from OPT containing fructose (batch I) and mannitol (V) were statistically significant ($P < 0.01$). Further when drug release profiles from all the five OPTs were compared with the profile of marketed conventional (Xenobid?) tablet as shown in Fig. 1, it was observed that all the OPT exhibited comparatively controlled and prolonged drug release as compared to the marketed tablet.

Sodium lauryl sulfate (SLS) is a non-swelling wicking agent which has the ability to draw water into the porous network of a delivery device. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area (Rudnic *et al.* 2000). To study the effect of SLS on release profiles of NS, OPT with SLS were prepared (batch VI) using fructose as osmogen and its release profile was compared with batch I without SLS in Fig. 2. A significant ($P < 0.05$) difference in the rate and extent of drug release from batches I and VI was observed. Drug release from batch VI containing SLS was much higher than batch I without SLS. Further, to study the effect of sodium bicarbonate (SBC) on release profile of NS, OPT with SBC was prepared (batch VII) and its release profile was compared with batch I OPT without SBC (Fig. 2), while both batches contained fructose as osmotic agent. The batch VII with SBC gave significantly higher ($P < 0.05$) drug release than batch I without SBC. The lag phase was also avoided due to presence of SBC in the core of OPT (batch VII). Such observation is explained as SBC apart from acting as an osmotic agent also has a beneficial buffering capacity which maintain pH of the core towards alkaline side, thereby augmented the solubility of NS. This increased solubility of drug coupled with the stepped osmotic pressure gradient created by dual osmotic agents (fructose along with SBC) have led to relatively increased rate and extent of drug release from batch VII. NS, being weakly acidic drug, may precipitate after delivery in the gastric fluid (acidic pH) and may block the orifice as well as may deposit on the exterior wall of the membrane, which may ultimately slow down both the drug delivery rate through orifice and also the imbibition rate of imbibing fluid in the core through the membrane.

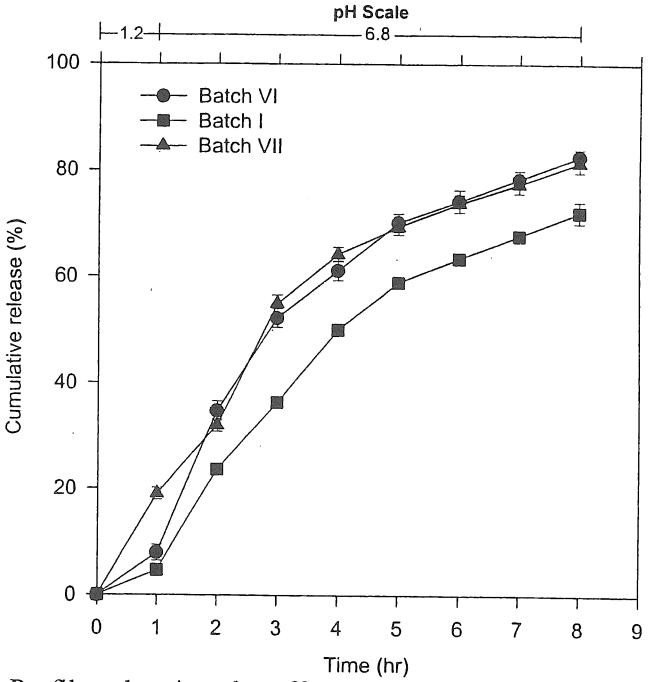

Fig.2 Profiles showing the effect of sodium lauryl sulphate and sodium bicarbonate on NS release from OPT in sequenced GI fluid at 50 rpm. Bars represent ±S.D. (n=3).

The presence of effervescent agent like SBC in core is expected to dissolve such precipitated drug, clearing the orifice and membrane and thus help in normal functioning of the OPT with drug release without any hindrance caused by precipitated drug .

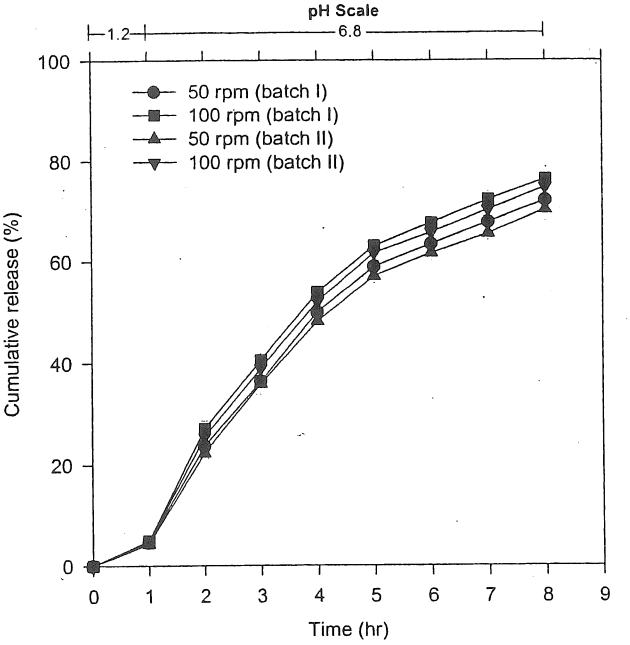

Fig.3. Profiles showing the effect of agitation intensity on NS release from OPT batches I and II in sequenced GI fluid. Bars represent ±S.D. (n=3).

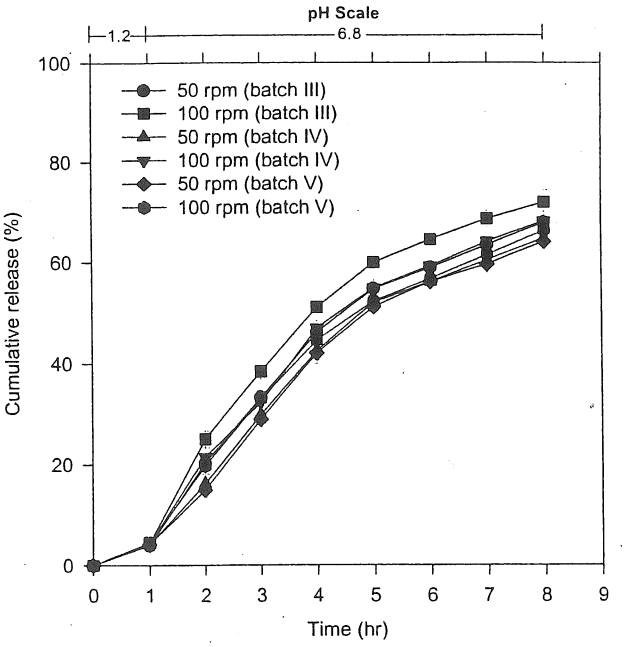

Fig.4. Profiles showing the effect of agitation intensity on NS release from OPT batches III ,IV and V in sequenced GI fluid. Bars represent ±S.D. (n=3).

The OPT batches I to V were also tested in vitro at 100 rpm in addition to 50 rpm, to investigate the effect of agitation intensity on NS release characteristics from OPT. The drug release profiles shown in Fig. 3 and 4 clearly show non-significant ($P > 0.01$) difference in rate and extent of NS release at 50 and 100 rpm from all the batches of OPT. This indicates that motality of GIT will have negligible effect on rate and extent of drug release and is possible due to osmotically driven release from the OPT. The findings of this study led us to conclude that the rate and extent of NS release were found to be dependent on different osmotic agents, sodium lauryl sulphate and sodium bicarbonate in the core formulation of EOP and independent on the agitation intensity of release medium. Further the developed EOP of NS gave controlled and prolonged drug release in comparison to the conventional commercial tablet of NS.

References

Brodgen R.N., Heel R.C., Speight T.M. and Avery G.S. (1979). Naproxen up to date a review of its pharmacological properties and therapeutic efficacy and use in rheumatic disease and pain states. *Drugs* 18: 241-277.

Lachman L., Cooper J. (1963). A programmed automated film coating process. *J. Pharm. Sci.* 52: 490-496.

Mody D.S., Scott M.W., Lieberman H.A. (1964). Development of a simple automated film coating procedure. *J. Pharm. Sci.* 53: 949-952.

Mroszceak E., Yee T.P., Bynum L. (1988). Absorption of naproxen controlled release tablets in testing and postprandial volunteers. *J. Clinical Pharmacol.* 28: 1128-1131.

Ozdemir N., Sahin J. (1997). Floating dosage forms. *Int. J. Pharm.* 158: 91-97.

Ramakrishna, N., Mishra, B. (2002). Plasticizer effect and comparative evaluation of cellulose acetate and ethylcellulose-hydroxypropylmethylcellulose combination coatings as semipermeable membranes for oral osmotic pumps of naproxen sodium. *Drug Dev. Ind. Pharm.* 28:403-412.

Rose S., Nelson J.F. (1955). A continuous long term injector. *Aust. J. Exp. Biol.* 33: 415-420.

Rudnic, Edward M., Burnside, Beth A., Flanner, Henry H., Wassink, Sandra E., Couch, Richard A., Pinkett, Jill E. (2000). Osmotic Drug Delivery System. U.S. Patent 6110498.

Santus G., Baker R.W. (1995). Osmotic drug delivery: a review of patent literature. *J. Contrl. Rel.* 35: 1-21.

Theeuwes F. (1975). Elementary osmotic pump. *J. Pharm. Sci.* 64: 1987-1997.

Theeuwes F., Higuchi T. (1972). Osmotic dispensing device for releasing beneficial agent. US Patent No. 3845770.

Verma R.K., Mishra B. (1999). Studies on formulation and evaluation of osmotic pumps of nimesulide. *Pharmazie* 54: 74-75.

Zentner G.M., Rork G.S., Himmelstein K.J. (1990). Controlled porosity osmotic pump. US Patent No. 4968507.

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