containing 15 μmol/l β-diketone, 50 μmol/l tri-n-octyl-phosphine oxyde (TOPO), 0.1% Triton X-100, and 0.1 nmol/l europium (III) in 0.1 M acetate buffer pH 3.2. The obtained solution was mixed well and the fluorescence was measured at 615 nm. The dose-response standard curve was constructed by plotting the ratio B/Bo against the concentration of pefloxacin. The obtained curve was used for the determination of unknown drug concentrations in serum.

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Studies on formulation and evaluation of oral osmotic pumps of nimesulide

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The purpose of this communication is to report the findings of an attempt to develop an oral osmotic pump (OP) of nimesulide (NE). The elementary osmotic pump (EOP) consists of an osmotic core having drug surrounded by a semipermeable (SP) membrane and an orifice [1]. When the EOP reaches the gastro intestinal tract (GIT), the core imbibes GI fluid at a constant rate determined by membrane permeability and osmotic pressure inside the core. For a system at constant internal volume, the EOP delivers, in any time interval, a volume of saturated drug solution equal to the volume of solvent uptake. The drug delivery rate remains contant as long as excess solid is present inside the device.

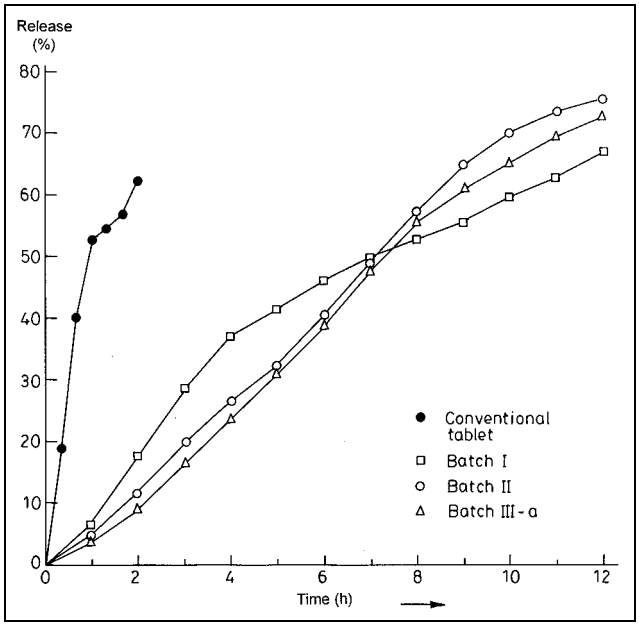

Fig.: Cumulative percent release profiles of EOP's of NE in comparison to conventional tablets

NE, a potent NSAID, is a poorly water soluble (~0.01 mg/ml) drug [2] and is associated with problems of frequent administration and GI disturbances when given in conventional formulations. Generally, EOP is well suited for drugs of intermediate water solubility [3]. However, by use of buffers along with the drug, it is possible to modulate the drug's solubility and thus to formulate EOP of poorly water soluble drugs [4]. Based on the above facts, this study was aimed towards the develop-

Table: Formula, data (mean ±SD) for different parameters and time to release 30% ($t_{30\%}$) and 60% ($t_{60\%}$) NE from different formulations

Ingredients (quantity in mg/tab)	Batch. No. of formulations				
	I	II	III-a	III-b	III-c
Nimesulide	100	100	100	100	100
SBC	–	50	20	20	20
Coated SBC	–	–	80	80	80
DSP	100	100	–	–	–
NaCl	200	200	–	–	–
KCl	–	–	300	300	300
SLS	12	15	15	15	15
Talc	4	5	5	5	5
PVP	8	9	10	10	10
Coating nature	SP	SP	SP	SP*	MP
Hardness kg/cm^2 (n = 3)	8.00 ± 0.72	8.21 ± 0.96	8.46 ± 0.09	8.46 ± 0.09	8.46 ± 0.09
Thickness before coating, mm (n = 10)	4.26 ± 0.98	4.61 ± 1.21	5.01 ± 0.68	5.01 ± 0.68	5.01 ± 0.68
Weight variation, mg (n = 20)	430 ± 1.96	491 ± 0.96	550 ± 1.21	552 ± 0.96	549 ± 1.09
Coating thickness, μm (n = 3)	200 ± 0.46	215 ± 0.72	208 ± 1.21	208 ± 0.98	209 ± 1.21
Content of active ingredient, mg (n = 5)	102.48 ± 1.08	101.72 ± 2.18	99.92 ± 0.96	99.92 ± 0.96	99.92 ± 0.96
Orifice diameter, μm (n = 5)	320.67 ± 0.43	321.00 ± 0.42	320.21 ± 0.58	320.19 ± 1.21	–
$t_{30\%}$ (h)	3.2	4.6	4.8	6.8	2.6
$t_{60\%}$ (h)	10.2	8.4	8.8	**	5.7

SBC: Sodium bicarbonate; Coated SBC: Sodium bicarbonate coated with 10% w/w cellulose acetate phthalate in acetone; DSP: Disodium hydrogen phosphate dihydrate; SLS: Sodium lauryl sulphate; PVP: Poly vinyl pyrolidone; SP: Semipermeable (coating with 2% w/w cellulose acetate in acetone); SP* Semipermeable (coating with 2% w/w ethyl cellulose in ethanol); MP: Microporous (coating with 2% w/w solution of cellulose acetate/sorbitol/PEG 400 (10 : 7.5 : 1) by parts dissolved in acetone; ** Not achieved

ment of an OP of NE which can deliver the drug with a controlled rate for longer duration in order to achieve better therapeutic benefits with improved patient compliance and minimum side effects.

Different OP data for 30% ($t_{30\%}$) and 60% ($t_{60\%}$) drug release are shown in the Table. Release profiles are shown in the Fig. Conventional tablets (Nimulid®) delivered the drug faster and $t_{30\%}$ and $t_{60\%}$ were achieved in 0.5 and 1.85 h, respectively. The OP delivered the drug with a comparatively slower but almost constant rate for 12 h.

In our earlier investigation, when OP does not contain DSP and SBC, but contained NaCl, only 4% of NE release was observed in 12 h and was attributed to the poor water solubility of the drug. So, NE solubility was modulated by incorporation of different buffers in the osmotic core, and much higher drug releases were observed from batch I (65%), II (75%) and IIIa (71%) in 12 h. Batches II and IIIa exhibit more controlled drug release profiles than batch I.

Drug release data shown in the Table indicate that formulation IIIc coated with a microporous membrane gave faster and higher (73% in 12 h) drug release than OP IIIa and IIIb coated with SP membranes. Batch IIIa coated with cellulose acetate gave a higher (71% in 12 h) drug release than IIIb (42% in 12%) coated with ethyl cellulose. This is attributed to the lower water permeability of ethyl cellulose compared to cellulose acetate [5]. A portion of SBC was coated with enteric coating polymer CAP in batches IIIa, IIIb and IIIc, with an idea to make available uncoated SBC for dissolution of NE in the stomach and coated SBC for dissolution of NE in intestine so as to achieve a constant delivery rate of NE in all parts of the GIT.

Thus, we conclude that poorly water soluble drugs like NE can be formulated well as potential prolonged and controlled release OP using an optimum amount of selective osmotic agents and buffers.

Experimental

NE was a gift of Recon Ltd, India. Nimulid® (100 mg) tablets (Panacea Biotech Ltd. India), best quality chemicals and polymers were purchased.

Each batch size of tablets was 500. All the materials (Table) were passed through sieve no. 60 (mean dia. 250 µm), granulated using a 2% w/w ethanolic solution of PVP, dried, mixed with SLS and talc and compressed on a Manesty E2 tableting machine using 11 mm standard concave punches. Tablets were coated in standard coating pan (Edwards and Co., London) using a coating solution as described in the Table and dried overnight at 40 ± 2 °C. An orifice was drilled through all SP coated OP using microdill [6].

All the OP were evaluated for various parameters as shown in the Table and were evaluated *in vitro* (5 runs for each batch) on an USP XXI dissolution apparatus II using 900 ml of pH 7.4 phosphate buffer maintained at 37 ± 0.5 °C and stirred at 50 r.p.m. Withdrawn samples were analysed on a Jasco UV/VIS spectrophotometer (model 7800) at 394 nm, the actual concentration of NE in the samples were read from a calibration curve prepared from pure NE in pH 7.4 phosphate buffer.

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Effects of *Quercus ilex* L. and *Punica granatum* L. polyphenols against ethanol-induced gastric damage in rats

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Local traditional medicine uses widely tannins-rich plants against gastric discomfort and diarrhea, among these plants are *Quercus ilex* roots bark and *Punica granatum* fruit peel. Crude extracts of some medicinal plants of which the main constituent is tannin prevent formation of gastric lesions induced by HCl, ethanol, indomethacin, reserpine and serotonin [1, 2]. Several polyphenols including tannic acid, ellagic acid, flavone, flavanone and quercetin have been reported to protect the stomach against necrotizing agents [3–6]. In this study, we examine the effects of polyphenols extracted from *Quercus ilex* roots bark and *Punica granatum* fruit peel on ethanol-induced gastric damage in rats.

In control animals, 15 min treatment with absolute ethanol were sufficient to induce extended hemorrhagic lesions mainly in the glandular region of the stomach. Animal pretreatment with *P. granatum* and *Q. ilex* polyphenols led to a marked dose-dependent protection of the stomach (Fig.). The number of lesions was slightly reduced but

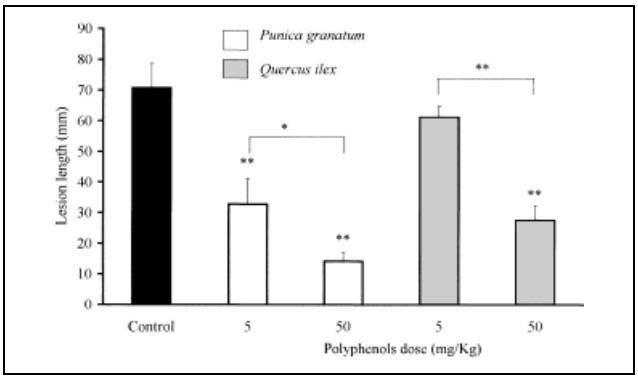

Fig.: Effect of polyphenols extracted from *Punica granatum* fruit peel and *Quercus ilex* roots bark on ethanol-induced gastric lesions in rats. Bars are means + SEM. $^{*}P < 0.05$; $^{**}P < 0.001$

without reaching a significant level ($P > 0.05$). However, both the severity and the length of the lesions were reduced. The protection afforded by *Q. ilex* was observed only with the high dose (60% protection). Total lesions length was reduced by both doses of *P. granatum* polyphenols; the percent protection was 53 and 80% for 5 and 50 mg/kg respectively.

The observed results are in agreement with previous reports showing gastroprotective effects of plant polyphenols [3–6]. The difference in efficiency of *P. granatum* and *Q. ilex* extracts is probably due to differences in their composition and/or in concentration of the same active molecule(s). The mechanisms underlying cytoprotection by polyphenols seems to reinforce the gastric defence barrier: (a) inhibition of the parietal proton pump [4], (b) stimulation of mucus secretion [7] probably by increasing prostaglandin E2 production [8], (d) maintenance of an efficient blood supply [2].

Experimental

Quercus ilex L. roots bark was collected from Babor National Park (Algeria). *Punica granatum* L. fruit peel was collected from fruits available on